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IN THE UNITED STATES SUPREME COURT

MARK MILLER AND CHERYL MILLER, INDIVIDUALLY AND MARK MILLER, AS ADMINISTRATOR OF THE ESTATE OF MATTHEW MILLER, DECEASED,

Petitioners,

v.

PFIZER, INC. (ROERIG DIVISION),

Respondent.

ON PETITION FOR WRIT OF CERTIORARI FOR THE UNITED STATES COURT OF APPEALS FOR THE TENTH CIRCUIT

PETITION FOR WRIT OF CERTIORARI

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QUESTIONS PRESENTED FOR REVIEW

1. What standards should a district court employ when it appoints independent experts or technical advisers to assist in its "gatekeeping" responsibilities, and specifically, is it an abuse of discretion to deprive the court's own experts of the most current and available scientific information?

2. Whether the courts below erred by ignoring the on-going, developing scientific evidence linking Zoloft to suicide, and, specifically whether the FDA's March 22, 2004, pronouncement that Pfizer should warn about the potential association between Zoloft and suicide merits either an outright reversal or GVR?

Certificate of Interested Persons

The undersigned counsel of record certifies that the following listed parties have an interest in the outcome of this case. These representations are made in order that the Justices of this Court may evaluate possible disqualification or recusal.

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REPORTS OF OPINIONS

The district court entered numerous interlocutory opinions or orders in this case, some of which are published online on Westlaw and/or LEXIS. The first was its November 10, 1999 order denying Pfizer's motion to either strike the complaint or permit Pfizer to file a general denial. It is published at *Miller v. Pfizer, Inc.*, 1999 WL 1063046 and 1999 U.S.Dist. LEXIS 18345 (D.Kan. 1999).

Other orders are unpublished, like the district court's June 27, 2000, order refusing on First Amendment grounds to "gag" the Millers and preclude them from speaking out publically about the association between Zoloft and suicide. Further, its June 12, 2000 order denied Pfizer's motion to strike semi-final witness list or, the alternative, to strike witnesses whose testimony is not described, and decrying said motion as a tactic which "degrades the legal profession and the practice of law."

Orders specifically at issue in this Petition, include the district court's August 18, 2000, Order to Show Cause why independent experts should not be appointed, which is published at 2000 U.S. Dist. LEXIS 20640 (Note: dated December 2000 in LEXIS), and its April 24, 2001, Order Appointing Independent Experts, which is apparently unpublished. Because of the importance of these two Orders to the issues raised by this Petition, see App. 9-10.

The two opinions which lead to summary judgment for Pfizer are published at *Miller v. Pfizer, Inc.* 196 F.Supp.2d 1062 (D. Kan. 2002), and *Miller v. Pfizer, Inc.* 196 F.Supp.2d 1095 (D. Kan. 2002). App. at 1-2. The Tenth Circuit's opinion affirming the summary judgment for Pfizer is published at *Miller v. Pfizer*, 356 F.3d 1326 (10th Cir. 2004). App. at 3.

GROUNDS FOR JURISDICTION OF THE UNITED STATES SUPREME COURT

The United States Court of Appeals for the Tenth Circuit delivered its opinion on February 4, 2004. This Court has discretionary jurisdiction pursuant to 28 U.S.C. §1254(1).

STATEMENT OF THE CASE

This Kansas diversity jurisdiction case involves the tragic death by suicidal hanging of Matthew Miller, a 13-year old boy. In July 1997, seven days before his death, a doctor who, unbeknownst to the boy's parents, was paid by Pfizer to give speeches hawking Zoloft, prescribed the SSRI drug Zoloft for Matt.

The legal case involves the preclusion of testimony from Dr. David Healy, the world's foremost expert on the issue of antidepressant-induced suicidality. Dr. Healy has passed every other *Daubert* challenge in federal cases around the country on this same issue. Indeed, this expert has testified before, or provided information directly to, regulators in both the United Kingdom and the United States on the SSRI/suicidality issue. Both countries have, thereafter, required warnings to be issued about an association between the SSRIs and suicide. Specifically, and most recently, on March 22, 2004, consistent with Dr. Healy's research and testimony, the FDA recommended that Pfizer include a "warning" in the Zoloft label, alerting doctors and patients that they should watch closely for "the emergence of suicidality." App. at 5-6.

Zoloft is a psychoactive, antidepressant drug in the Selective Serotonin Reuptake Inhibitor [SSRI] class. The other two most well-known drugs in this class are Prozac and Paxil.

The scientific evidence linking these drugs with an increased risk of suicide, particularly for children and adolescents, has been mounting for years. Developments within the last year before the decision of the Tenth Circuit include June 2003 announcements by the British Medicines Control Agency (MCA) and U.S. Food and Drug Administration (FDA) that Paxil may pose an increased risk of suicide for children and adolescents; and an August 22, 2003, announcement by the maker of the similar drug Effexor, warning that it, too, increases

the risk of suicide for children and adolescents. Specific to Zoloft, in December 2003 the British MCA "contraindicated" Zoloft for children and adolescents, finding that the data regarding Zoloft "show a consistently higher incidence of suicidal thoughts and self-harm in children and adolescents" and that "the commonest reason for discontinuation of treatment was suicidal thoughts/self-harm." The Millers asked the Tenth Circuit to take judicial notice of these on-going developments, but the court denied the requests.

On Monday, February 2, 2004 – two days before the Tenth Circuit's affirmance in this case – two advisory panels of the FDA heard evidence from over 60 witnesses concerning the link between SSRI drugs and increased suicidality in children and adolescents. Later that evening, the panels took the extraordinary step of issuing their own warnings to "put a speed bump in the road" regarding the use of this class of medications in children and adolescents, once again, in large measure, because of the risk of suicide. *See* FDA.Advisory Committee, *Antidepressants Strengthen Warnings About Pediatric Suicidality Risk Needed Immediately, Cmte. Says*, <http://fdaadvisorycommittee.com/FDC/AdvisoryCommittee/Committees/Anti-Infective+Drugs/020204_Suicide/020204_SuicideR.htm> (Feb. 2, 2004). App. at 5-6.

Then, finally, as noted above, on March 22, 2004, the FDA itself issued a Public Health Advisory, recommending that all of the manufacturers of these drugs, including Pfizer, "include in their labeling a Warning statement that recommends close observation ... [for] the emergence of suicidality." *See* FDA Public Health Advisory, *Subject: Worsening Depression and Suicidality in Patients Being Treated with Antidepressant Medications*, <http://www.fda.gov/cder/drug/antidepressants/AntidepressantsPHA.htm> (March 22, 2004). App. at 5-6. As with the prior continuing scientific and regulatory developments, these matters

are appropriate for judicial notice by this Court. Rule 201(f), Fed.R.Ev.

The saga continues to unfold. In the wake of the FDA's ruling, information has emerged indicating that the FDA itself muzzled its own medical review officer, who intended to tell the February 2004 panels that his review of the companies' own data disclosed an increased risk of suicide, and that, in turn, has prompted two congressional investigations into the concealment of this problem from the public eye. *See* Joe Barton, *Barton, Greenwood Seek Info From FDA on Antidepressants*, <http://energycommerce.house.gov/108/Letters/0324204_1242print.htm> (March 24, 2004). App. at 7.

Realizing that the District of Kansas' local rules provide for a four-month discovery period, and anticipating the Defendant's *de rigeur Daubert* motion to exclude the testimony of Plaintiffs' principal causation expert, Dr. David Healy (a highly credentialed Irish neuro-psychopharmacologist with extensive peer-reviewed publications on point), prior to the initial Rule 16 conference in November 1999, the Millers provided a preliminary disclosure report from Dr. Healy and requested that the district court appoint independent experts to help evaluate the scientific reliability of the opinion testimony from **both** parties. The Millers expected that early appointment of such experts would allow full discovery, discussion and rebuttal of the scientific arguments of both sides so that the independent experts could have access to all of the pertinent information and could properly advise the court concerning scientific reliability, based on a fully-developed record, tailored towards their questions.

In all honesty, they also expected that careful scrutiny of **both** parties' experts would reveal the hypocrisy in the drug manufacturer's "scientific" arguments and demonstrate that, if any expert's opinion failed *Daubert* muster it would be that of Pfizer's principal expert, Dr. J. John Mann of Columbia

University. Specifically, they knew that Dr. Mann's only **peer-reviewed** publications began with a lamentation about iatragenic suicide and included statements of concern about the "small vulnerable sub-population" of patients who might be at risk for increased suicidality as a result of these drugs. Dr. Mann also advocated warnings about this risk. Mann & Kapur, *The Emergence of Suicidal Ideation and Behavior During Antidepressant Pharmacotherapy,* Arch. Gen. Psychiatry, 48: 1027 (1991).

They also knew that the hypothesis of a causal relationship between SSRI drugs and suicidality was **testable**, and that Dr. Mann's article articulated four different ways to test prospectively. *Id.* In addition, they also knew that neither Pfizer nor any other SSRI manufacturer had conducted such tests.

Plaintiffs knew as well that one causal chain, SSRI drugs trigger akathisia which, in turn, increase the risk of suicide *i.e.*, was not only acknowledged in both peer-review articles and sworn testimony by Dr. Mann, but was also rapidly becoming **generally accepted**. *See* AMERICAN PSYCHIATRIC ASSOC., DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS, DSM-IV-TR, §333.99, which effectively codifies this causal chain. App. at 8. This standard reference text was subsequently cited by federal Judge Donetta Ambrose in her May 30, 2002 Opinion rejecting a *Daubert* challenge to Dr. Healy in *Cassidy v. Eli Lilly*, Civil Action 821, U.S.D.C. (W.D.Pa. May 30, 2002, Ambrose, C.J.). Judge Ambrose synopsized succinctly that Dr. Healy's "theory," *i.e.*, that SSRI drugs trigger suicidality in a small subpopulation of patients "has attended **general acceptance** in the relevant scientific community." *Id.* at p. 10.

Unfettered scientific inquiry by truly independent, "neutral" and objective experts would disclose all of these things.

Unfortunately, although the issue was raised at the initial Rule 16 scheduling conference, the district court did not rule on the Millers' motion until 18 months later. By that time, the discovery deadline had passed, Dr. Healy had been deposed, Pfizer had challenged his testimony based on a number of arguments, some of which ultimately turned out to be totally ill-founded, and the district court below had raised several extra-*Daubert* questions of its own as to which it wanted independent advice. Even more unfortunate was the district court's subsequent decision to subjugate the wording of Rule 703 and the interests of justice to a mechanistic application of Rule 26 and judicial expediency.

As a consequence, the district court refused to allow Plaintiffs' counsel to provide the independent experts with all of the incriminating internal documents – hidden from public scrutiny via the court's own "protective order – and to allow Dr. Healy or Plaintiffs' counsel to address concerns raised by the court's independent experts. In this regard, the court itself became an unwitting accomplice in the concealment which is even at the current time under congressional investigation. The independent experts' frustration regarding the limited information available to them is perhaps best illustrated by the following colloquy which occurred during the *Daubert* hearing:

DR. DAVIS: ... I think it's pretty clear that Dr. Healy is a distinguished clinician and has many publications so that he would meet that type of criteria. . . . And it may be an evolving field and that, so there is a matter of judgment. . . . And what I anticipated when I came today that Dr. Healy might present his calculations or there might be a lot of discussions of the techniques of the calculations. . . .

THE COURT: Maybe I can shed some light on this, especially in regard to your comment that you may be

> expected to hear some more full explanation of where the 2.19 figure was derived. This is part of where the intersection of law and science is maybe not clear to somebody coming in from the outside. But under our federal rules which govern pretrial proceedings, each side obviously has a chance to call their own experts who will testify, and there's a time set as part of the discovery process where each expert is required to produce a written report that states all of the opinions that that expert will offer at the trial, and also the basis for the opinions. That has to be done by a certain time prior to trial. . . . So that's why, that's what my ruling was earlier, and that's why you haven't heard the Power Point presentation that was alluded to earlier.

App. at 00579-00614, Doc. No. 552, Transcript of Proceedings, November 20, 2001, P.M. session, filed 11/30/00, at 389-92.

Based on the uninformed opinions and unanswered concerns of the independent experts, and totally ignoring corroborating evidence, like the **UN**published May 1996 admission by Pfizer in a report to the FDA that Zoloft had, indeed, triggered the suicidal attempt of one young patient, the district court became the first court in the nation to exclude the testimony of Dr. Healy, on matters squarely within his specialty. Her decision in this regard is in conflict with several other reported and unreported district court opinions.

Summary judgment for Pfizer necessarily followed and the Tenth Circuit affirmed.

Interestingly, the district court's decision in this regard was handed down more than eight months after the verdict and judgment in another SSRI wrongful death case. In *Tobin v. SmithKline Beecham Pharms.*, 164 F.Supp.2d 1278 (D.Wy.

2001), appeal dism'd pursuant to settlement, (10th Cir. 2002), the jury found that "Paxil can cause some people to become homicidal and/or suicidal." Plaintiffs' expert in that case was the same Dr. Healy excluded by the district court in this case, and SmithKline Beecham's expert was the same Dr. Mann who had been designated by Pfizer to testify in the district court in this case. In its published post-trial opinion, as well as in an earlier pretrial ruling, the *Tobin* court rejected *Daubert* challenges to Dr. Healy's general and specific causation opinions.

ARGUMENT

> ***The search is not a search for scientific precision. We cannot hope to investigate all the subtleties that characterize good scientific work. . . . Furthermore, science itself may be highly uncertain and controversial with respect to many of the matters that come before the courts. . . . The law must be fair. One important procedural safeguard . . . is the right to a trial by jury. Any effort to bring better science into the courtroom must respect the jury's constitutionally specified role.***[1]

Pfizer's response to this Petition is easy to anticipate: "the case involves a discretionary ruling by a district judge and the petition emphasizes events which occurred after that ruling and were, therefore, not before the judge at the time."

Although there is a certain ineluctable facial appeal to this view, the circumstances of this case present the classic confrontation between *Fairness* and *Finality*. Courts at all

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[1] Breyer, Introduction, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE (2nd ed., 2000)[hereinafter "REFERENCE MANUAL."]

levels in the judicial process must balance these oft-times competing considerations, but must necessarily do so in a manner that is consistent with the ultimate paradigm of Rule 1, Fed.R.Civ.P., to do what is "just." Or, as Justice Breyer stated in the REFERENCE MANUAL, "the law must be fair." *Id.* at 4.

Judges sometimes differ about those circumstances in which finality must yield to fairness. But the Justices of this Court have recently expressed unanimity in their opinion that "intervening developments" of a significant nature merit reconsideration in light of the most current information. *Lawrence v. Chater*, 516 U.S. 163 (1996)(granting summary GVR pursuant to 28 U.S.C. §2106 so that lower courts can consider implications of new position by a federal agency). The FDA's March 22, 2004, warnings edict places the case at bar squarely within the holding and rationale of *Lawrence*. App. 5-6.

No decision ever rendered by this Court has spawned more litigation in the lower courts or more citations in appellate opinions than *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579 (1993). A *Daubert*-based exclusionary motion is *de rigeur* tactics in every pharmaceutical case, no matter how strong the opinion evidence may be or how the expert himself is qualified. Indeed, numerous speakers at CLE functions have opined that defense counsel's failure to file such a motion may well subject him to claims of malpractice. This, in turn, puts a horrendous burden on the courts and on other litigants, particularly in a jurisdiction like Kansas where artificial caps on certain categories of damages enable wealthy defendants to literally spend plaintiffs like the Millers totally out of any meaningful judicial remedy.

There are some arenas in which the scientific evidence is developing. This case presents just such an arena. At the time this suit was initially filed, the published scientific literature directly on point was not terribly extensive. Much of

it, including Pfizer expert Dr. Mann's own article cited *supra*, and a 2000 article by Donovan and colleagues (which found that Zoloft had a relative risk of "deliberate self-harm" which was 4.4x higher than the index drug and did so with a *Daubert* "rate of error, *i.e.*, a "p-value" of .001) was supportive of the plaintiff's case.[2] But the issues were still being debated in many circles. More importantly, due to the pharmaceutical companies' failure to test the most pertinent information possible was non-existent. Additionally, the most damning evidence against Zoloft and its sister drugs was **unpublished**.[3] The scientific world is, indeed, only just now beginning to realize that the truly incriminating evidence regarding SSRI-induced suicidality has been withheld from public scrutiny. *See e.g., Data from Unpublished Trials Suggest that Most SSRI Antidepressant Drugs Unsuitable for Children*, LANCET (April 24, 2004)("The story of research into SSRI use in childhood depression is one of confusion, manipulation, and institutional failure.")[4]

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[2] *See* Stuart Donovan et al., *Deliberate self-harm and antidepressant drugs: Investigation of a possible link*, 177 Brit. J. Psychiatry 551-556 (2000).

[3] Not only has Pfizer refused to publish all of its data relating to Zoloft and suicide, it has also done everything within its power to deprive the public of access to this information and thereby conceal the danger. For example, even after it neglected to mark the critical May 1996 admission document discussed herein as "confidential," it tried like crazy to retrieve it and put it under wraps. As noted above, it also tried to "gag" the Millers and their counsel. And, most ironically, it actually succeeded in depriving the court's own experts of the most damning internal documentation of this lethal side effect.

[4] Craig J. Whittington, et al., *Selective Serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data*, 363 The Lancet 9418 (April 24, 2004) <http://www.thelancet.com/journal/vol363/iss9418/full/llan.363.9418.original_research.293>.

The FDA itself has exemplified the "institutional failure" of which the LANCET speaks. In May 1996, Pfizer filed a document reviewing incidents of suicidality in children and adolescents taking Zoloft. This was 14 months before Matt Miller's death. And, yet, the FDA ignored this damning admission and other evidence of incipient dangers for nearly seven years. Even in 2004, when public pressure forced it to schedule hearings, it muzzled its own chief scientific reviewer who had planned to sound a public alarm about SSRI-induced suicidality. This "institutional failure" has now even precipitated a congressional investigation into the concealment of the problem. *See* Joe Barton, *Barton, Greenwood Seek Info From FDA on Antidepressants*, <http://energycommerce.house.gov/108/Letters/0324204_1242print.htm> (March 24, 2004). App. at 7.

What do these matters have to do with the case at bar? Simply this. The district court below totally ignored Pfizer's admission that Zoloft had triggered a suicide attempt of one minor patient. This critical admission corroborated Dr. Healy's opinion on general causation. The evidence in the court below also demonstrated without question and even without the subsequent developments that Dr. Healy's opinion passes muster under both *Daubert* and *Kumho Tire Co. v. Carmichael*, 526 U.S. 137 (1999). Significantly, by "freezing the record" and specifically striking an exhibit which would summarize Pfizer's internal admissions, the district court also deprived its own experts of critical information.

The threshold question is, of course, "is this case *cert.*-worthy"? In the last decade this Court has written three major opinions concerning the district court's "gatekeeping" role under Rules 702-03. The first was, of course, *Daubert* itself. The Court took *cert.* in that case " in light of sharp divisions among the courts regarding the proper standard for the admission of expert testimony." *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 585 (1993). As noted above, there are "sharp

divisions" between the district court below on the one hand and at least four other district courts across the land regarding the admissibility of Dr. Healy's opinions on SSRI-induced suicidality.

Four years later the Court decided *General Elec. Co. v. Joiner*, 522 U.S. 136 (1997). In this instance *cert.* was granted, not to resolve a conflict in the lower courts, but rather "to determine what standard an appellate court should apply in reviewing" a *Daubert* decision. *Id.* at 138-39.

Finally in *Kumho*, *cert.* was granted "in light of uncertainty among the lower courts about whether, or how, *Daubert* applies to expert testimony that might be characterized as based not upon 'scientific' knowledge, but rather upon 'technical' or 'other specialized' knowledge." 526 U.S. at 146-47.

Thus, this Court exercised discretionary jurisdiction in all three cases to provide guidance to the lowers courts on how to decide and review critical decisions regarding expert testimony. From that perspective, this case cries out for *certiorari*.

Five years have passed since the Court's last writing on this important topic, and as this case itself amply illustrates, the courts below continue to flounder. Uncertainty is still rampart, and the lower courts continue to need guidance. Moreover, although the case law concerning independent experts is sparse, it is clear that there is a **conflict** between the way that the courts are handling such experts. For example, compare the case at bar, in which the experts' were hamstrung by very limited access to information with the extensive scientific inquiry in *Hall v. Baxter Healthcare Corp.*, 947 F.Supp. 1387 (D.Or. 1996). Specifically, in that case Judge Jones allowed the independent experts (whom he appointed pursuant to Rule 104 rather than Rule 706), (a) to review "voluminous" materials

submitted by both parties (apparently with no restrictions or censorship by the court), and (b) to hear the testimony of **both sides'** experts in each field. *Id.* at 1394. Moreover, because the hearing was conducted under Rule 104, Judge Jones permitted no evidentiary objections. *Id.* This is in stark contrast to Judge Vratil's numerous rulings in the *Daubert* hearing in the case at bar, at which she precluded Dr. Healy from providing answers to questions by the experts themselves and information within his knowledge and possession.

The case at bar presents a proper and timely forum for providing guidance regarding independent scientific experts, whether they are appointed pursuant to Rule 104, Rule 706, or some other authority. The "interim developments" merely ice the cake and underscore the true justness of the Millers' plight.

Justice should be based on the best available science. However, if the juridical history of *Daubert* itself illustrates nothing, it should tell both the Bench and the Bar that scientific orthodoxy is **not** the standard. The pharmaceutical industry argued for litmus tests. General acceptance. Or, if not that, peer review. But this Court rejected their arguments. Merrell Dow lost *Daubert*!

The law must accommodate developing scientific evidence, particularly where, as here, much of the most important information on point is withheld by industry from public scrutiny.

Many people have suggested that independently appointed scientific experts or technical advisers can help courts to sort the wheat from the chaff. Indeed, Justice Breyer's separate opinion in *Joiner* encouraged lower courts and litigants to use such resources. His subsequent introduction to the Second Edition of the REFERENCE MANUAL echoed those recommendations and emphasized that, properly used, this procedure should be "neutral, in principle favoring neither

plaintiffs nor defendants." *Supra* at p.7. If it is, then courts, litigants, and the scientific community itself will be encouraged to work together towards genuine truth and justice. On the other hand, if the result in this case -- on an issue that is obviously one of enormous and timely public health import -- is to set the standard, then future litigants and scientists[5] will be very loathe to proceed in this fashion.

The Millers heeded Justice Breyer's advice. It was not Pfizer who asked the court to appoint independent experts. It was the Millers themselves. Pfizer went along, kicking and screaming, *i.e.*, the experts were appointed over Pfizer's objections. But a procedure which should have been scientifically rigorous became legally turgid. The experts did not "neutrally" focus on both sides experts or scientific issues which they themselves found significant. Rather, Pfizer set the agenda through its *Daubert* motion and the Court then restricted the scope of inquiry and information which the experts could consider. Rule 26 trumped Rule 703, and the experts' scientific questions, even as to those points, were unanswered. Moreover, the real point of methodological criticism, *i.e.*, whether Dr. Healy's "relative risk" calculations could be replicated, focused on a Pfizer contention which both the independent experts and the court below found to be misguided. Sadly, in the end, the Millers were hoisted on their own petard, and the memory of their only son's life was sacrificed on the altar of Pfizer's profits and judicial expediency.

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[5] The independent experts in this case were not told what the ramifications of their opinions would be. Only later did they learn that their scientific critique and comments resulted in the exclusion of testimony from a highly qualified colleague and the deprivation of a day in court for the Miller family. One can only imagine how mortified they must have been on March 22, 2004, when the FDA itself ruled that Pfizer should warn about this very side effect. App. 5-6.

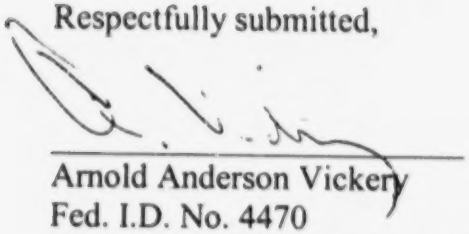
CONCLUSION

Other parents who have lost a child to SSRI-induced violence have had their day in court. And they had it with benefit of the expert testimony of Dr. Healy. Tim Tobin was awarded $2 million as a result of the SSRI-precipitated death of his daughter Alyssa. *Tobin v. SmithKline Beecham Pharms., supra.* If Pfizer follows the FDA's March 22, 2004 recommendation, parents in the future will also be forewarned about the potential of Zoloft to cause their teenagers to take their own lives. App. 5-6. This will save lives.

But in the meantime, what is to become of Mark and Cheryl Miller and their quest for justice? What will the Highest Court in the Land say to them? Too bad? Too late? Tough stuff? OR, will the Court find that justice is far too precious a commodity to be relegated to "gotcha" status?

For the foregoing reasons, we urge the Court to grant *certiorari* in this case and consider the case upon its full merits and in light of the most current and authoritative information available to date. As an alternative, and particularly in light of the FDA's recent awakening, the Court could GVR the case as it did in *Lawrence, supra,* and remand with instructions that the district court should reconsider its *Daubert* decision in light of all information currently available at the time that the court rules.

Respectfully submitted,



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PROOF OF SERVICE
CERTIFICATE OF SERVICE

Pursuant to Rule 29.3 of the Rules of the Supreme Court of the United States, I certify that three copies of the Petition for Writ of Certiorari have been served upon counsel named below via certified mail, return receipt requested, on this 30th day of April, 2004:

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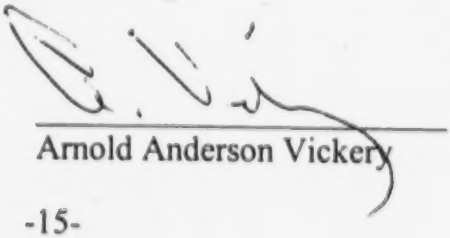

Arnold Anderson Vickery

SUPREME COURT
FILED

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OFFICE OF THE CLERK

NO. _____

IN THE UNITED STATES SUPREME COURT

MARK MILLER AND CHERYL MILLER, INDIVIDUALLY AND MARK MILLER, AS ADMINISTRATOR OF THE ESTATE OF MATTHEW MILLER, DECEASED,

Petitioners,

v.

PFIZER, INC. (ROERIG DIVISION),

Respondent.

ON PETITION FOR WRIT OF CERTIORARI FOR THE UNITED STATES COURT OF APPEALS FOR THE TENTH CIRCUIT

APPENDIX TO PETITION FOR WRIT OF *CERTIORARI*

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LEXSEE 196 FSUPP2D 1062

MARK MILLER AND CHERYL MILLER, INDIVIDUALLY AND MARK MILLER AS ADMINISTRATOR OF THE ESTATE OF MATTHEW MILLER, DECEASED, Plaintiffs, v. PFIZER INC (ROERIG DIVISION), Defendant.

CIVIL ACTION No. 99-2326-KHV

UNITED STATES DISTRICT COURT FOR THE DISTRICT OF KANSAS

196 F. Supp. 2d 1062; 2002 U.S. Dist. LEXIS 2298; CCH Prod. Liab. Rep. P16,292

February 7, 2002, Decided

DISPOSITION: [**1] Defendant's motions to exclude testimony sustained in part, overruled in part; motion to exclude sustained; opposition to plaintiffs' request for independent expert verification sustained; request for sanctions overruled.

CASE SUMMARY:

PROCEDURAL POSTURE: Plaintiff parents claimed their son committed suicide because he took a selective serotonin (SSRI) reuptake inhibitor manufactured by defendant company. The parents sought to hold the company liable for failure to warn and marketing misrepresentations under a common law negligence theory and the Kansas Products Liability Act. The matter was before the court on motions regarding the parents' primary expert witness.

OVERVIEW: The expert proposed to testify, among other things, that the SSRI could cause depressed patients to commit suicide (general causation) and that it did so in the case of the son (specific causation). The expert's view as to general causation was distinctly a minority view. The company argued that his opinions and methodologies were unreliable and inadmissible under Fed. R. Evid. 106, 403, 702, and 703. The court found glaring, overwhelming, and unexplained

inconsistencies in the expert's methodologies and in the application of factors designed to assist in determining general causation and whether a drug may cause a certain chain reaction. Thus, the expert's testimony on general causation, premised on those methodologies, was excluded from evidence. Consideration of such evidence would have confused and misled the jury and wasted the parties' time and resources. Because the court sustained the company's motion to preclude the expert from testifying as to general causation, and the expert was the parents' only expert on the subject, the issue of specific causation was, for all practical purposes, moot. The expert's testimony on the issue of specific causation was inadmissible.

OUTCOME: The court adopted the independent experts' report, and sustained in part the company's motions to exclude the expert's testimony and for sanctions against the expert for violations of the court's protective order. The court sustained the company's motion in limine to exclude the use of three studies. The court sustained the company's post-hearing requests in part, and overruled them in part, and overruled the parents' post-hearing request.

LexisNexis (TM) HEADNOTES - Core Concepts:

Evidence > Witnesses > Expert Testimony
[HN1] Fed. R. Evid. 702 provides that a witness who is qualified by knowledge, skill, experience, training or education may testify in the form of opinion or otherwise as to scientific, technical or other specialized knowledge if such testimony will assist the trier of fact to understand the evidence or to determine a fact in issue, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

Evidence > Procedural Considerations > Preliminary QuestionsEvidence > Witnesses > Expert Testimony
[HN2] Under the Daubert decision, a district court must determine at the outset, pursuant to Fed. R. Evid. 104(a), whether expert testimony is reliable and will assist the trier of fact to understand or determine a fact in issue. In determining

whether a particular scientific theory or technique is reliable, the district court may consider several non-dispositive factors: (1) whether the proffered technique can and has been tested; (2) whether the technique or theory has been subject to peer review; (3) the known or potential rate of error; and (4) the general acceptance of a technique in the relevant scientific community. The proponent of expert testimony must show a grounding in the methods and procedures of science which must be based on actual knowledge and not subjective belief or unaccepted speculation. An expert's qualifications are relevant to the reliability inquiry.

Evidence > Witnesses > Expert Testimony
[HN3] Randomized controlled trials and large-scale epidemiological studies are not essential to the formation of an expert opinion as to causation.

Evidence > Witnesses > Expert Testimony
[HN4] Publication (which is but one element of peer review) is not a sine qua non of admissibility; it does not necessarily correlate with reliability, and in some instances well-grounded but innovative theories will not have been published. Some propositions, moreover, are too particular, too new, or of too limited interest to be published. But submission to the scrutiny of the scientific community is a component of "good science," in part because it increases the likelihood that substantive flaws in methodology will detected. The fact of publication (or lack thereof) in a peer reviewed journal thus will be a relevant, though not dispositive, consideration in assessing the scientific validity of a particular technique or methodology on which an opinion is premised.

Evidence > Witnesses > Expert Testimony
[HN5] Use of a small number of challenge-dechallenge studies to test a hypothesis is inadequate and not generally accepted methodology.

Evidence > Witnesses > Expert Testimony
[HN6] Even if an expert is not legally required to show a relative risk of at least 2.0, he must rely on studies which yield results

that are statistically significant regarding the causal relationship at issue in the case.

Evidence > Hearsay Rule & Exceptions > Business Records
[HN7] Grade cards that schools keep in the ordinary course of business are exceptions to the hearsay rule under Fed. R. Evid. 803(6).

Evidence > Witnesses > Expert Testimony
[HN8] Fed. R. Evid. 703 states that the bases for opinion testimony need not be admissible.

Evidence > Witnesses > Expert Testimony
[HN9] Fed. R. Evid. 702 mandates that the court determine the admissibility of expert testimony, but Fed. R. Evid. 703 allows for opinion testimony.

Evidence > Witnesses > Expert Testimony
[HN10] Merely possessing a medical degree is not sufficient to permit a physician to testify concerning any medical-related issue.

Evidence > Procedural Considerations > Inferences & PresumptionsEvidence > Witnesses > Expert Testimony
[HN11] The plaintiffs have the burden of establishing the admissibility of their expert's opinions.

Evidence > Witnesses > Expert Testimony
[HN12] In determining whether an expert may testify concerning the adequacy of a warning label, the dispositive question is whether the adequacy of the warning is within the reasonable confines of the expert's subject area.

Torts > Products Liability > Duty to Warn
[HN13] Whether or not a given warning is adequate depends upon the language used and the impression that it is calculated to make upon the mind of an average user of the product.

Evidence > Witnesses > Expert Testimony
[HN14] The reliability of expert testimony concerning the adequacy of a warning label is extremely questionable when the

expert failed to design and test a proposed warning and could not point to contrary industry practice.

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JUDGES: Kathryn H. Vratil, United States District Judge.

OPINIONBY: Kathryn H. Vratil

OPINION: [*1064]

MEMORANDUM AND ORDER

Mark and Cheryl Miller claim that their 13-year-old son, Matthew, committed suicide because he took Zoloft, a prescription drug which Pfizer Inc. manufactured for the treatment of depression. See Amended Complaint (Doc. # 92) filed December 16, 1999. In that regard, plaintiffs seek to hold Pfizer liable for failure to warn and marketing misrepresentations under common law negligence theory and the Kansas Products Liability Act, K.S.A. § 60-3304. See Pretrial Order (Doc. # 171) filed March 6, 2000. This matter comes before the Court on various motions regarding plaintiffs' primary expert witness, Dr. David Healy: Defendant Pfizer Inc's Refiled Motions To Exclude The [**3] Testimony Of Dr. David Healy And For Sanctions Against Dr. David Healy For Violations Of The Court's Protective Order (Doc. # 534) filed November 1,

2001; Plaintiffs' Post-Hearing Memorandum, And Request For Independent Expert Verification (Doc. # 545) filed November 27, 2001; Defendant Pfizer Inc.'s Opposition To Plaintiffs' Post-Hearing Memorandum And Request For Independent Expert Verification; Request For Sanctions (Doc. # 547) filed November 29, 2001; and Defendant Pfizer Inc's Motion In Limine No. 9 To Exclude The Use At Trial Of The Hindmarch Study, Dr. Healy's "Healthy Volunteer Study," And Dr. Healy's Statistical Analysis Of The Pfizer Meta-Analysis (Doc. # 304B) filed April 28, 2000. After carefully considering the parties' arguments and briefs in support, the Court is ready to rule.

Background n1

n1 Plaintiffs' response to defendant's motion to exclude includes a section titled "Statement of Facts." Defendant does not respond to these purported facts, most of which are actually legal argument disguised as factual statement. The Court need not deem these facts admitted, however, because a response to such facts is only required for a summary judgment motion. See D. Kan. Rule 56.1.

[**4]

Sertraline hydrochloride is a selective serotonin reuptake inhibitor ("SSRI") drug which is generically known as sertraline. Pfizer markets it as Zoloft. Dr. David Healy, a Welsh psychiatrist and academic neuropsychopharmacologist, proposes to testify that Zoloft can cause depressed patients to commit suicide and that it did so in the case of Matthew Miller. In his declaration of May 9, 2000, Dr. Healy states that his opinion is based upon "research that went into . . . aforementioned publications, review of depositions and testimony in the Fentress v. Eli Lilly case, depositions and trial testimony in the Forsyth v. Eli Lilly case, exhibits in both cases, depositions in the Miller v. Pfizer case, thousands of pages of Pfizer documents, the "healthy volunteer" study I conducted, as well as published and unpublished clinical trial material of which I was in possession." n2 In an article titled Zoloft And Suicide: Causal Mechanisms, which is attached to his declaration of August 13, 1999, Dr.

Healy cites 54 depositions, exhibits and articles on which he has also relied. Because Dr. Healy has explained the basis for his opinions in this manner, he has [*1065] opened an almost [**5] limitless arena of material for the Court to review in evaluating the admissibility of his testimony. Of course this is precisely the situation which the mandatory disclosure requirements of Fed. R. Civ. P. 26(a)(2) seek to avoid. See Burton v. R.J. Reynolds Tobacco Co., 203 F.R.D. 636, 639 (D. Kan. 2001). Nonetheless the Court has carefully reviewed every article in the record which Dr. Healy has cited in his various declarations. Aside from Dr. Healy's own articles, none of them directly support his claim that Zoloft causes akathisia, which in turn causes suicide in depressed patients. For the purposes of the pending motions, the Court focuses on the articles and research that Dr. Healy has authored or on which he appears to place particular emphasis: his own "Healthy Volunteer Study," his statistical analysis of pre-existing Pfizer data (the so-called Pfizer "Meta-Analysis"), his application of Koch's Postulates, and his evaluation of three studies - one by Dr. Ian Hindmarch (the so-called "Hindmarch Study") and two challenge-dechallenge-rechallenge studies by other authorities.

n2 Healy Declaration of May 9, 2000 (Exhibit 2) in Index Of Plaintiffs' Consolidated Exhibits To Pretrial Motions, Vol. II ("Plaintiffs' Pretrial Ex., Vol. II") (Doc. # 369) filed May 12, 2000 at P8. Although Dr. Healy notes in his declaration of May 9, 2000 that he has utilized material from another lawsuit, he does not specify the particular material on which he has relied.

[**6]

Dr. Healy is an accomplished researcher in the area of neuropsychopharmacology, and his credentials are not in dispute. Indeed, he is an eminent psychiatrist and neuropsychopharmacologist who has made important contributions to the history of psychiatry and many significant clinical contributions. n3 Notwithstanding his credentials, Pfizer asks the Court to exclude Dr. Healy's opinions, along with certain studies and calculations on which he relies - the

Hindmarch Study, the Healthy Volunteer Study, and the Pfizer Meta-Analysis. Pfizer does not seek to exclude the two challenge-dechallenge-rechallenge studies, although it does discount them as "case reports" and "anecdotal evidence."

n3 Transcript Of November 19, 2001 Hearing ("Transcript") (Doc. # 550) filed November 30, 2001 at 8.

To assist the Court in evaluating Dr. Healy's opinions under Daubert v. Merrell Dow Pharm., Inc., 509 U.S. 579, 125 L. Ed. 2d 469, 113 S. Ct. 2786 (1993), the Court appointed two independent experts: [**7] John Concato, M.D., M.S., M.P.H. and John M. Davis, M.D. n4 Dr. Concato, a professor at the Yale University School of Medicine, is a general internist and clinical epidemiologist who is a preeminent authority in his field. n5 Dr. Davis is a professor in the department of psychiatry at the University of Illinois at Chicago; he has practiced in the field of neuropsychopharmacology since 1965, spending seven years with the National Institute of Mental Health. He was one of the first scientists to study affective disorders and the theory that reserpine can lead to suicide. n6 Dr. Davis was a member of the FDA's Psychopharmacological Drug Advisory Committee ("PDAC") which examined the initial drug application for Zoloft, n7 and concluded that it was safe and effective for the treatment of depression. n8

n4 See Order Appointing Independent Experts (Doc. # 486) filed April 24, 2001. Dr. Davis and Dr. Concato rendered invaluable service in this case and the Court is extremely grateful for their assistance.

n5 Transcript (Doc. # 550) at 93-94.

n6 Id. at 4-6.

n7 Id. at 72. [**8]

n8 See PDAC Transcript (Exhibit FF) in Appendix To Defendant's Partial Summary Judgment On Plaintiffs' Failure To Warn Claim, Vol 3 ("Pfizer's Failure To Warn Appendix, Vol. 3") (Doc. # 226) filed April 18, 2000 at 117.

On September 5, 2001, after reviewing materials which the parties jointly submitted, the experts submitted their Report Of Independent Experts (Doc. # 502) ("Independent Expert Report"). On November [*1066] 19 and 20, 2001, the Court held a Daubert hearing at which the parties had an opportunity to question the experts and present other relevant evidence.

Legal Standard

[HN1] Rule 702, Fed. R. Evid., provides that a witness who is qualified by knowledge, skill, experience, training or education may testify in the form of opinion or otherwise as to scientific, technical or other specialized knowledge if such testimony will assist the trier of fact to understand the evidence or to determine a fact in issue, "if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness [**9] has applied the principles and methods reliably to the facts of the case." n9

n9 This statement of the rule incorporates the amendment effective December 1, 2000. The Court uses its discretion under 28 U.S.C. § 2074(a) to apply the amended rule since the new language codifies the existing standards for Rule 702 and does not represent a substantive change in the law.

Analysis

I. Defendant's Motions To Exclude Dr. Healy's Testimony (Doc. # 534) And Use At Trial Of The Hindmarch Study, The Healthy Volunteer Study And The Pfizer Meta-Analysis (Doc. # 304b)

Dr. Healy proposes to testify about (1) general causation (that Zoloft causes suicide); (2) specific causation (that Zoloft caused Matthew Miller to commit suicide); (3) suicidology and the incidence of teen suicide; (4) the adequacy of Pfizer's warnings about Zoloft; and (5) the regulation of pharmaceuticals by the FDA. n10

n10 Dr. Healy's opinion, as it has evolved throughout this litigation, can be found in his Rule 26 Statement of August 13, 1999 ("First Rule 26 Statement"), contained as Exhibit 91 in the Appendix Of Exhibits (Nos. 86-99) To Defendant Pfizer Inc's Pretrial Motions ("Pfizer's Pretrial Ex. Nos. 86-99") (Doc. # 232) filed April 18, 2000, including a document by Dr. Healy titled Zoloft And Suicide: Causal Mechanisms, which is part of Dr. Healy's First Rule 26 Statement; his Rule 26 Statement of December 10, 1999 ("Second Rule 26 Statement"), contained as Exhibit 48 in Appendix Of Exhibits (Nos. 26-51) To Defendant Pfizer Inc's Pretrial Motions ("Pfizer's Pretrial Ex. Nos. 26-51") (Doc. # 229) filed April 18, 2000; the Declaration Of David Healy, M.D. dated May 9, 2000, contained as Exhibit 2 in Index Of Plaintiffs' Consolidated Exhibits To Pretrial Motions, Vol. I ("Plaintiffs' Pretrial Ex., Vol. I") (Doc. # 368); his Letter Report of March 6, 2000 attached as Exhibit G in Memorandum Of Law In Support Of Defendant Pfizer's Motion In Limine No. 9 To Exclude The Use At Trial Of The Hindmarch Study, Dr. Healy's "Healthy Volunteer Study," And Dr. Healy's Statistical Analysis Of The Pfizer Meta-Analysis ("Pfizer's MIL No.9 Memorandum") (Doc. # 304C) filed April 28, 2000; and his deposition on March 27 and 28, 2000, Deposition Of David T. Healy, M.D., attached as Exhibit C to Pfizer's MIL No. 9 Memorandum (Doc. # 304C).

In his First and Second Rule 26 Statements, Dr. Healy expresses his belief that through the mechanisms of akathisia and emotional indifference, Zoloft in general can "make an individual who may not have been likely to commit suicide before taking the pill, more likely to do so while on a course of treatment." In support of this opinion, Dr. Healy cites (1) case reports in the literature (of which he was the senior author on one); (2) two extensive reviews of the topic of antidepressant-induced suicidality which he authored in 1994 and 1999; (3) his doctoral thesis; (4) an epidemiological study (in which he was involved) to calculate rates of suicide in primary care mood disorders; (5) interviews with senior figures in the field of psychopharmacology, gathered as a history of antidepressants; and (6) his Healthy Volunteer Study.

Dr. Healy's article titled Zoloft And Suicide: Causal Mechanisms, which is part of his First and Second Rule 26 Statements, is a rambling and largely disjointed discourse which basically purports to overthrow randomized controlled trials [RCTs] and epidemiological studies as the "gold standard" for demonstrating cause and adverse effect relationships between sertraline and suicide, and enthrone Koch's Postulates in their place. Dr. Healy's politics on this issue are evident as he claims that "as regards RCTs and causality, the single greatest role RCTs and epidemiological studies are likely to play in cases of SSRI induced suicidality are to stand as an expensive assessment technologies [sic] that only pharmaceutical corporations have the ability to employ," and that "the portrayal of these methods as gold standards owes everything to a strategy which involves occupying the playing field rather than one which in actual fact delivers what is claimed for it."

In his declaration of May 9, 2000, Dr. Healy attempts to answer criticisms which Pfizer has lodged against his various opinions and methodologies. Primary topics of discussion include (1) the structure and results of his Healthy Volunteer Study; and (2) his claim to have conducted a Meta-Analysis of Pfizer data, yielding a relative risk calculation of 2.19 for Zoloft versus placebo and an increased relative risk of 2.05 in studies conducted specifically on children. The balance of Dr. Healy's declaration is more argument and invective than scientific in nature.

In his letter report of March 6, 2000, Dr. Healy states that his review of "the Pfizer suicide collection of documents" very strongly supports his prior opinions. In particular, he cites evidence that healthy volunteers became so agitated on Zoloft that they had to discontinue its use; that Pfizer had internally used a challenge-dechallenge paradigm when assessing causality; and that in Pfizer's own assessment Zoloft has induced suicidality in young children.

[*1067]

[**10]

A. General Causation

Dr. Healy's view as to general causation is a distinctly minority view. The American College of Neuropsychopharmacology, the FDA's PDAC, and the Medicines Control Agency in his own United Kingdom have all reached contrary conclusions. n11 For this reason and others, Pfizer argues that Dr. Healy's opinions and methodologies are unreliable and inadmissible under Daubert and Federal Rules of Evidence 106, 403, 702 and 703. n12

n11 Independent Expert Report (Doc. # 502) at 2.

n12 In part, Pfizer complains that Dr. Healy's opinions were developed in the course of anti-Zoloft litigation. In Daubert v. Merrell Dow Pharm., Inc., 43 F.3d 1311, 1317 (9th Cir. 1995), the Ninth Circuit placed considerable emphasis on this factor in addition to those which the Supreme Court enumerated in Daubert v. Merrell Dow Pharm., Inc., 509 U.S. 579, 125 L. Ed. 2d 469, 113 S. Ct. 2786 (1993). The additional factor is not particularly useful, however, in this case. One would not expect Dr. Healy to opine before this lawsuit that Zoloft caused Matthew Miller to commit suicide. On the other hand, Dr. Healy has been alleging for years that drugs like Zoloft generally cause suicide. See, e.g., David Healy and William Creaney, Fluoxetine And Suicide, 303 Brit. Med. J. 6809, 1058-59 (Oct. 26, 1991) (editorial letter); David Healy, The Fluoxetine And Suicide Controversy, 1 CSN Drugs 223-231 (1994).

[**11]

In concluding that Zoloft causes suicide in some patients, Dr. Healy relies heavily upon case reports and his own studies and calculations, and disavows the need for randomized controlled trials ("RCTs") and epidemiological studies. n13 His opinion rests most heavily on his own Healthy Volunteer Study, his Meta-Analysis of Pfizer data (which allegedly yields a relative risk calculation of 2.19), his application of Koch's Postulates, and his evaluation of three studies - the Hindmarch Study and two challenge-dechallenge-rechallenge studies. n14 Because these studies are critical [*1068] to an understanding of his testimony, they are briefly summarized as follows:

n13 See August 13, 2000 Healy Declaration (Exhibit 91) in Pfizer's Pretrial Ex. Nos. 86-99 (Doc. # 232) at 0000083.

n14 Dr. Healy also relies on conversations with Dr. Paul Leber (former head of the Central Nervous System division of the FDA, which is responsible for licensing Zoloft, and the deposition of Dr. Douglas Geenens (Matthew Miller's treating physician), and a plethora of articles in the medical literature - all of which speak for themselves. Because these materials do not confirm Dr. Healy's hypothesis that Zoloft causes akathisia, which in turn causes suicide in depressed patients, these materials do not directly factor into the Daubert analysis. For purposes of this order the Court generally ignores them and focuses on the original work by Dr. Healy which - when read against the backdrop of his conversations and review of depositions and medical literature - purports to directly connect Zoloft and suicide through the medium of akathisia.

[**12]

Healthy Volunteer Study: In 1999, Dr. Healy conducted a double-blind study of 21 healthy volunteer health care workers from the North Wales Department of Psychological Medicine in Bangor, Wales, of which Dr. Healy is the director. n15 Dr. Healy and his research assistant recruited the subjects from administrative, medical and nursing staff who ranged in age from 28 to 52 years. According to Dr. Healy, none were on concurrent drug treatment, all were free of medical conditions and none had a history of psychiatric illness. Under the study, each volunteer took either sertraline (Zoloft) or reboxetine n16 for 15 days. After this period, the volunteers were drug-free for two weeks. For the next 15 days, each volunteer switched and used the other drug. None of the subjects had suicidal ideation while taking reboxetine. During the second regimen, two volunteers who were taking Zoloft developed "clear suicidal ideation" (one of which reached "extremely serious proportions"), along with elements of akathisia and emotional blunting. Akathisia is "[a] syndrome characterized by an inability to remain in a sitting position, with motor restlessness and a feeling of muscular quivering. [**13] " n17 Other subjects had these features but did not become suicidal. The study did not use

a placebo control. Because of the nature of the study, it involved extensive interaction between research personnel and participants during the study and afterwards in focus groups; furthermore, the volunteers were "more or less aware" of Dr. Healy's views and the fact that he expected them to react more poorly on Zoloft than on reboxetine.

n15 Dr. Healy first referred to this study on December 10, 1999, in his Second Rule 26 Statement, when he noted that data from this study was still being analyzed and should be available for peer review and inspection in February of 2000. On February 1, Dr. Healy produced limited materials, consisting of a draft article entitled Emergence of Antidepressant Induced Suicidality and daily reports from two volunteers who had taken part in the study. At the time of his deposition on March 27 and 28, 2000, Dr. Healy had not completed his analysis and he did not claim that the results of his study were statistically significant.

The study was designed for 20 volunteers, one of whom dropped out after one week on reboxetine and was then replaced with another subject. [**14]

n16 Reboxetine is a norepinephrine reuptake inhibitor which is used to treat depression. See Attorney's Medical Deskbook (3rd ed. 2000). The FDA has not approved reboxetine for sale in the United States.

n17 Stedman's Medical Dictionary (26th ed. 1995) at 41.

Meta-Analysis of Pfizer Data: On April 15, 2000 - after Dr. Healy's deposition and four iterations of expert reports in this case - plaintiffs filed their second supplemental responses to Pfizer's first requests for admissions. n18 At that time they first disclosed that Dr. Healy had completed a "meta-analysis" of Pfizer data and that his review indicated a "relative risk of suicidal acts on Zoloft, compared to placebo and corrected for exposure times of 2.19 (i.e. 2.31 vs. 1.0555)." According to plaintiffs, Dr. Healy's analysis was as follows:

n18 See Plaintiffs' Second Supplemental Responses, Per Order Of The Court To Defendant Pfizer Inc's First Requests For Admissions (Exhibit N) to Pfizer's MIL No.9 Memorandum (Doc. # 304C).

[**15]

All Zoloft treated MDD cases - 23 suicidal acts in 6,549 subjects = 2.31% per year; All TCA treated - 2 suicidal acts in 922 subjects = 1.37% per year; All placebo treated - 3 suicidal acts in 1,042 subjects = 1.055% per year.
[*1069]
The Court cannot locate in the record a more precise explanation of Dr. Healy's calculation. It may derive from premarketing clinical trials for Zoloft which set forth data and incidence rates for suicides and suicide attempts in Zoloft-treated, placebo-treated and active-control-treated depressed patients. It may derive from reports which Pfizer provided the FDA in connection with its application to market Zoloft for the treatment of pediatric patients with obsessive compulsive disorder. Neither the Pfizer experts nor the independent experts have been able to replicate the calculation.

Koch's Postulates: Koch's Postulates are a series of factors which are designed to assist in determining general causation and whether a drug may cause a certain reaction. The factors are strength of association, consistency with other research, alternative explanations, temporal relationship, biological plausibility, specificity of association and dose-response [**16] relationship. Reference Manual On Scientific Evidence ("Reference Manual") (1st ed. 1994). n19 In his analysis of Koch's Postulates, Dr. Healy did not attempt to directly assess whether Zoloft causes suicidal ideation or behavior. Instead he focused on whether SSRI drugs have a favorable therapeutic effect on depressive disorders (Dr. Healy concluded that the strength of this association is "in fact . . . rather weak") and the link between SSRI drugs and akathisia (Dr. Healy concluded that this association was much stronger, if not conclusive). He therefore concluded that "there is greater specificity in the

relationship between SSRI and akathisia than there is between the SSRI and the response of a depressive disorder."

n19 The second edition of the Reference Manual was issued during the pendency of this litigation Earlier orders refer to the first edition but the Court will also refer to the second edition where applicable. This order will distinguish the two by including the edition and year in its citations.

[**17]

With regard to the association between SSRI drugs and akathisia, based on his application of Koch's Postulates, Dr. Healy concluded that (1) as to strength of association, akathisia is a clear-cut event which is strongly associated with some insult to the central nervous system such as an infective process or drug intake and, in the case of Zoloft, akathisia may occur in at least a mild form in over 50 per cent of the patients who are taking the drug; (2) as to temporal relationship, akathisia has a fairly predictable temporal onset in relation to the intake of Zoloft, i.e. 24 to 48 hours following the institution of treatment or an escalation of dose (a phenomenon which builds to a peak over one to two weeks as the drug dosage rises in the body); (3) as to biological plausibility, there appears to be a "clear biological mechanism" by which SSRI drugs produce akathisia; n20 (4) as to specificity of association, not all antidepressants appear capable of producing akathisia and "there is . . . greater specificity in the relationship between an SSRI and akathisia than there is between the SSRI and the response of a depressive disorder;" and (5) as to dose-response relationship, [**18] there appears to be a clear dose-response relationship between SSRI intake and akathisic phenomena. Dr. Healy did not address two postulates: consistency with other research and alternative explanations. On the other hand, he added four factors: salience of association, consistency of association, support by experiment and support by analogy. As to salience of association (which he explained as "the [*1070] difficulty in otherwise explaining the effect"), Dr. Healy stated that the association between SSRI drugs and akathisia may be "very salient," in that the patient may be visibly distressed and clearly deteriorated "with no . . . means

of explaining what is happening other than by invoking an action of a drug." As to consistency of association, Dr. Healy stated that akathisia has a physiological input which appears to occur across all personality types, and akathisia in response to a particular agent strongly predicts renewed akathisia on further exposure to the triggering agent. As to support by experiment, Dr. Healy stated that in his own tests, healthy volunteers who took droperidol all became akathisic and up to five became suicidal, with two becoming acutely suicidal within hours of [**19] treatment. Although Dr. Healy does not explain what droperidol is, or how it relates to this litigation, he posits that this experiment constitutes "strong evidence" in favor of the proposed mechanism of action whereby an SSRI may produce suicidality. Finally, as to support by analogy, Dr. Healy states that according to case reports, patients committed suicide on Prozac (another SSRI drug) and reserpine (a drug which is active on the serotonin system and according to Dr. Healy "probably" causes akathisia by similar mechanisms to Zoloft) even though they were "not depressed at all" and had "no nervous condition on which the suicide could be blamed." According to Dr. Healy, these case studies provide "strong evidence" of a causal relationship between SSRI intake and suicidality.

n20 Dr. Healy does not identify this "clear biological mechanism," other than to state that it can be "blocked or ameliorated" through drugs.

Hindmarch Study: In 1988, Dr. Ian Hindmarch conducted a double-blind placebo-controlled [**20] crossover study to assess the effects of sertraline (Zoloft), alone and with diazepam (Valium), on the psychomotor performance of 12 healthy volunteers at the University of Leeds, U.K. n21 On April 14, 2000, after Dr. Healy's deposition and various expert reports, plaintiffs served supplemental discovery responses. In plaintiffs' second supplemental responses to Pfizer's first requests for admissions, n22 they stated that according to Dr. Healy, the Hindmarch study demonstrated a relative risk greater than two for "emotional blunting" and probable aggressive, assaultive or suicidal behavior in persons taking Zoloft. These claims are not explained in the record, which reveals that (1) the Hindmarch

study dose began at 150 mg (three times more than the recommended 50 mg starting dose for Zoloft and three times more than the dose allegedly taken by Matthew Miller); (2) none of the volunteers had any diagnosed psychiatric condition; and (3) it appears that none of the study volunteers reported assaultive behavior, depression, akathisia, or homicidal or suicidal behavior, ideation or attempts.

n21 This study is aptly titled, A Double-Blind Placebo-Controlled Cross-Over Study To Assess The Effects Of Sertraline, Alone And With Diazepam, On Psychomotor Performance. Exhibit P in Pfizer's MIL No.9 Memorandum (Doc. # 304C). [**21]

n22 See Plaintiffs' Second Supplemental Responses, Per Order Of The Court To Defendant Pfizer Inc's First Requests For Admissions (Exhibit N) to Pfizer's MIL No.9 Memorandum (Doc. # 304C).

Challenge-Dechallenge-Rechallenge Articles: In concluding that Zoloft causes suicide, Dr. Healy relied upon two challenge-dechallenge-rechallenge studies. The first was a 1991 report by Anthony J. Rothschild, M.D. and Carol A. Locke, M.D., which discussed three patients (all of whom had histories of suicidal ideation) who made serious suicide attempts during treatment with fluoxetine (Prozac). n23 [*1071] During re-treatment with fluoxetine, all three developed severe akathisia - stating that the akathisia made them feel suicidal and, in the context of their depressive episodes, had precipitated their prior suicide attempts. The akathisia and suicidal ideation abated after fluoxetine was discontinued or propranolol (an anti-akathisia medication) was added. The authors noted that they had observed the emergence of suicidal ideation secondary to akathisia in only three of 1,500 patients (0.2%) - perhaps [**22] in part because they had lowered the fluoxetine dose when side effects developed and promptly recognized and treated the akathisia. They noted the hypothesis that suicidal ideation and suicide occur secondary to the emotional distress of akathisia, but also cautioned that "it remains unclear whether there exists a common pharmacologic basis for akathisia and suicidal ideation or acts." Because it is

"conceivable that the development of akathisia in patients with a past history of suicidal or homicidal ideation is particularly problematic," the authors added that "clinicians should remain alert to the development of akathisia in patients taking fluoxetine and to the fact that patients are often unable to distinguish akathisia from the ongoing symptoms of their psychiatric illness," i.e. patients need to be reassured that the symptoms are side effects of medication and are treatable.

n23 Re-exposure To Fluoxetine After Serious Suicide Attempts By Three Patients: The Role Of Akathisia, 52 J. Clin. Psychiatry 491-93 (1991).

[**23]

The second challenge-dechallenge-rechallenge study involved six case reports in an article by Dr. Robert King, et al. n24 In these reports, self-injurious ideation or behavior appeared or intensified during fluoxetine treatment of six patients, age 10 to 17 years, who were among 42 young patients receiving fluoxetine for obsessive compulsive disorder ("OCD"). Before they received treatment, four of the six patients had major risk factors for self-destructive behavior, including depression or prior suicidal ideation or self injury. The article examined three possible explanations for the emergence of suicidal ideation and self-destructive behavior in the six subjects: (1) that it was coincidental, in that while all six subjects had received fluoxetine, they all had complex long-standing psychiatric difficulties; (2) that it was a consequence of the treatment or was related to medication-induced agitation, disorganization or mood changes; and (3) that it was due to a specific effect of fluoxetine on the regulation of aggression directed either outward or toward the self. The authors concluded that while the adverse side effects appeared to be more than coincidental as to four of [**24] the six patients, "distinguishing among these three alternatives [was] not possible on the basis of the uncontrolled clinical material presented here." Accordingly, they suggested a need for more research. Pfizer first argues that Dr. Healy's testimony on general causation will not satisfy the pertinent indicia of scientific reliability or assist the trier of fact in this

case. [HN2] Under Daubert, a district court must determine at the outset, pursuant to Rule 104(a), whether expert testimony is reliable and will assist the trier of fact to understand or determine a fact in issue. See Daubert, 509 U.S. at 592. In determining whether a particular scientific theory or technique is reliable, the district court may consider several nondispositive factors: (1) whether the proffered technique can and has been tested; (2) whether the technique or theory has been subject to peer review; (3) the known or potential rate of error; and (4) the general acceptance of a technique in the relevant scientific community. Id. at 593-94. [*1072] The proponent of expert testimony must show "a grounding in the methods and procedures of science which must be based on actual knowledge [**25] and not subjective belief or unaccepted speculation." Mitchell v. Gencorp. Inc., 165 F.3d 778, 780 (10th Cir. 1999). An expert's qualifications are relevant to the reliability inquiry. See United States v. Taylor, 154 F.3d 675, 683 (7th Cir. 1998); In re Indep. Serv. Org. Antitrust Litig., 85 F. Supp. 2d 1130, 1163 (D. Kan. 2000).

n24 Emergence of Self-Destructive Phenomena in Children and Adolescents during Fluoxetine Treatment, 30 J. Am. Acad. Child Adolesc. Psychiatry 2, 179-186 (March 1991), attached as Exhibit 12 to Plaintiffs' Pretrial Ex., Vol. I (Doc. # 368).

1. Methodology

The first Daubert factor asks whether a theory is susceptibility to testing and whether the theory has been subjected to such testing. See Mitchell, 165 F.3d at 780 (citing Daubert, 509 U.S. at 593). Pfizer appears to concede that Dr. Healy's theory can be tested, but argues that it has not been tested because Dr. Healy [**26] has not conducted and does not rely on any RCT or large-scale epidemiological study which demonstrates a causal relationship between Zoloft and suicide in depressed patients. Absent such studies, Pfizer faults Dr. Healy for relying on tests which involve SSRI drugs *other* than Zoloft and drugs which are not even SSRI drugs *like* Zoloft, or which involve other patient populations or other adverse side effects or events. n25

n25 For purposes of this analysis, Pfizer cites no evidence which suggests a relevant difference between Zoloft and other SSRI drugs. Indeed in some instances Pfizer insists that because Zoloft is similar to other SSRI drugs, it - like the other SSRI drugs - does not cause suicide. Compare Memorandum In Support Of Defendant Pfizer Inc.'s Motion To Exclude Testimony Of David Healy ("Defendant's Exclusion Memorandum") (Doc. # 535) filed November 1, 2001 at 21 (chastising Dr. Healy for references to other SSRIs) and Defendant's Exclusion Memorandum (Doc. # 535) at 24-26 (reliance on studies of Prozac, another SSRI drug, for proposition that link to suicide has been refuted). Obviously Pfizer cannot have it both ways. The Court will consider evidence regarding other SSRI drugs, although such evidence may not be as weighty as that which directly concerns Zoloft.

The Court does disregard studies which concern non-SSRI drugs. On this record, studies of these drugs would appear to have limited utility since they are not shown to be comparable in operation or effect.

[**27]

Plaintiffs admit that Dr. Healy does not rely on the type of RCTs or large-scale epidemiological studies which Pfizer insists are requisite to an expert opinion as to causation, but they argue that his hypothesis has been otherwise tested in two challenge-dechallenge-rechallenge studies, his own Healthy Volunteer Study and Meta-Analysis of Pfizer data, as well as by Koch's Postulates. n26

n26 None of the parties discuss Koch's Postulates in the context of testing, and the Court proceeds on the assumption that because Koch's Postulates are basically a manner of reasoning, they cannot be "tested" in a logical or empirical sense.

Plaintiffs are correct that [HN3] RCTs and large-scale epidemiological studies are not essential to the formation of an expert opinion as to causation. See Bonner v. ISP Tech., Inc., 259 F.3d 924, 929 (8th Cir. 2001) (expert not required to rely on

epidemiological studies; testimony allowed when district court found expert reliance on temporal connection, animal studies, [**28] studies of chemicals with similar structures, study of drug at issue and the manner of acting on nerve pathways, and plaintiff's medical records showed reliable methodology under Daubert); Brasher v. Sandoz Pharm. Corp., 160 F. Supp. 2d 1291, 1296-98 (N.D. Ala. 2001) (expert testimony allowed despite lack of large-scale epidemiological study when experts relied on animal studies, case reports, Adverse Drug Reaction reports to FDA, generally accepted notion in the medical community and ruled out all other possible causes; [*1073] large-scale study nearly impossible because adverse reaction was rare event and study would unethically expose patients to risk of harm); Ruff v. Ensign-Bickford Indus., Inc., 168 F. Supp. 2d 1271, (D. Utah 2001) (lack of epidemiological data no bar to expert testimony that relied on numerous animals, discredited the one study relied upon by defendants and ruled out alternative causes).

At least as to Koch's Postulates, the independent experts do not disagree that Dr. Healy has identified a method of testing the potential cause-effect relationship of sertaline and suicide. n27 For purposes of this order the Court assumes that challenge-dechallenge-rechallenge [**29] studies, double-blind studies like Dr. Healy's Healthy Volunteer Study, and meta-analysis of data from randomized controlled trials or large-scale epidemiological studies are all legitimate tests which may be applied to determine whether Zoloft induces suicidal ideation or behavior. The Court therefore finds that Dr. Healy's hypothesis is amenable to testing and that he has at least identified tests which have some bearing on the issue of general causation. While Pfizer argues that his methodology is fatally flawed, that argument is addressed by Daubert's fourth factor, which the Court discusses below.

n27 Independent Expert Report (Doc. # 502) at 1.

2. Peer Review And Publication

The second Daubert factor asks whether the expert's theory or technique has been submitted to peer review and publication. Pfizer argues that Dr. Healy has not published any peer-reviewed article which states that Zoloft causes some people to commit suicide, and that his Meta-Analysis (including his relative risk [**30] calculation of 2.19) has not been subject to peer review. According to the independent experts, Dr. Healy is an accomplished investigator who has published several articles which are directly relevant to the issue of a possible association between sertraline and suicide, including Suicide In The Course Of The Treatment of Depression, 13 J. of Psychopharmacology 4-99 (1999), and Emergence Of Antidepressant Induced Suicidality, 6 Primary Care Psychiatry 23-28 (2000) (concerning Dr. Healy's Healthy Volunteer Study). n28 The experts characterize the first article as a "review" or "thought-piece" on possible mechanisms that would explain why patients commit suicide while taking antidepressants and the second article as "a randomized, controlled trial of two agents, given to 20 patients (total), that also included a component of qualitative analysis regarding changes in emotional state." n29 Although neither article proposed new or modified methods to determine causality and the editors and reviewers did not endorse Dr. Healy's methodology, both pieces were peer-reviewed and deemed suitable for publication. n30 Both articles theorize that SSRI drugs in general, and sertraline [**31] in particular, causes suicide in some patients. Pfizer is therefore incorrect in its argument that Dr. Healy has not published any peer-reviewed article which claims that Zoloft causes some people to commit suicide.

n28 Id.

n29 Id. at 1-2.

n30 Id. at 2.

On the other hand, Dr. Healy has not subjected to peer review his calculation, based on his Meta-Analysis of Pfizer data, that Zoloft carries a relative risk of suicide of 2.19. n31 Thus, while the theory behind Dr. Healy's work has been subject to limited peer review and publication, his relative risk calculation has not. n32

n31 Id. at 1.

n32 At the Daubert hearing, plaintiffs argued that Dr. Healy cannot subject his relative risk calculation to peer review since it is based on confidential data. Transcript (Doc. # 550) at 39-40. As the Supreme Court held, however, in Daubert,

[HN4] Publication (which is but one element of peer review) is not a sine qua non of admissibility; it does not necessarily correlate with reliability . . . and in some instances well-grounded but innovative theories will not have been published . . . . Some propositions, moreover, are too particular, too new, or of too limited interest to be published. But submission to the scrutiny of the scientific community is a component of "good science," in part because it increases the likelihood that substantive flaws in methodology will detected. . . . The fact of publication (or lack thereof) in a peer reviewed journal thus will be a relevant, though not dispositive, consideration in assessing the scientific validity of a particular technique or methodology on which an opinion is premised.

Daubert, 509 U.S. at 593-94. Regardless of the reason *why* Dr. Healy's numbers have not been subject to publication and peer review, the lack of peer review means that the Court simply does not have the assurance of reliability that this Daubert factor would normally provide.

[*1074]

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3. Rate Of Error And Proper Controls

Pfizer argues that Dr. Healy's Healthy Volunteer Study cannot properly form a basis for his opinions on causation because (1) it was not placebo-controlled test; (2) it did not result in a single suicide attempt; (3) its methodology has not been explained; (4) the sample size is too small to yield statistically significant analysis; (5) the cross-over design could lead to erroneous results; and (6) the volunteers were medical employees in the hospital department that Dr. Healy directed. To some degree, many of these problems result from the fact that the Healthy

Volunteer Study was not designed to research suicide but to test the effects of sertraline and reboxetine on the well-being of healthy subjects.

According to the independent experts, the lack of a placebo control in this context is not so much scientifically improper as it is problematic in evaluating the "big picture" question of a possible association between sertraline and suicide. n33 In other words, "when results from the study are extrapolated to the issue of sertraline possibly causing suicide, . . . a question can be raised what potential information is unavailable [**33] due to the absence of a placebo group . . . for example, . . . would patients receiving placebo have reported any fluctuations in their emotional state when asked to keep a diary, etc." The experts noted that although this scenario might seem unlikely, the absence of placebo controls "may affect the interpretation of the study findings."

n33 Independent Expert Report (Doc. # 502) at 16.

The independent experts also criticized the design of Dr. Healy's Healthy Volunteer Study in two important respects. First, its methodology involved intensive interaction between participants and research personnel, as well as a focus group at the end of the study - strategies which (along with a corresponding emphasis on patient narratives) represented qualitative rather than quantitative research. Second, because of the small sample size and the qualitative nature of the research, statistical analysis - while it theoretically could be done - would not produce a statistically significant result or provide a sufficient [**34] basis for calculating a statistically significant relative risk.

During the Daubert hearing, Dr. Healy admitted that his Healthy Volunteer Study was not designed to research treatment-emergent suicidality and that any conclusions regarding that phenomena were a by-product of the study results - not the design. He also acknowledged that his study was not well designed for relative risk calculations. Dr. Healy also agreed [*1075] with the independent experts that subliminal communication between the researchers and the volunteers may have influenced the results. In particular, before the study Dr.

Healy gave the subjects detailed information regarding the side effects of each drug. Subjects who had certain side effects might therefore deduce which drug they had received. n34 Dr. Healy also admitted that three subjects were on medication despite the fact that the research protocol was that the subjects would not be on medication, other than oral contraceptives. n35 In addition, even though the subjects allegedly had no histories of psychiatric illness, one of them had a history of depression. n36

n34 Dr. Healy defended this study design as a good way to ensure that subjects carefully monitored their mental states, but Pfizer s that this is not considered the proper way to conduct a study. See Transcript (Doc. # 551) at 333-35. [**35]

n35 See Transcript (Doc. # 551) at 309-11.

n36 She was not one of the two subjects who became suicidal on Zoloft. Id. at 313-15.

At the hearing, Pfizer took aim on the two subjects who allegedly had adverse effects on sertraline. Initial mental health examinations were not done on either volunteer. n37 Dr. Healy claimed that mental health screenings were supposed to be completed later, but did not address the fact that the researchers did not have a mental health base line for either subject. Furthermore, Dr. Healy could not rule out a carry-over effect from the reboxetine which the volunteers had taken before they started on Zoloft. n38 Dr. Healy opined that any reboxetine effect was probably small since reboxetine on its own did not cause agitation in any volunteer, but he did not address what effect reboxetine *with sertraline* may have had. Of the two volunteers who developed adverse reactions on sertraline, one lost her grandmother during the reboxetine period and during that time was unable to sleep or eat and felt annoyed, unhappy, miserable and angry. n39 The other [**36] felt terrible (like she had a flu bug) during the reboxetine period and she could not eat or sleep. Her bad experience on sertraline was preceded by a migraine headache, which Dr. Healy opines may have been drug-induced. n40

n37 Id. at 317-18.

n38 Id. at 319-20.

n39 Id. at 322-23.

n40 Id. at 328-29.

Dr. Healy did not defend the design of his Healthy Volunteer Study in a manner which adequately addresses the criticisms of Pfizer or the independent experts. The Court must therefore conclude that his Healthy Volunteer Study does not include controls sufficient to prove that Zoloft causes akathisia-induced suicide in depressed patients.

4. General Acceptance Of Methodology

Pfizer argues that the medical community does not agree that Zoloft causes suicide, and that Dr. Healy cannot testify otherwise. The "general acceptance" factor bears on the technique used, however, rather than the conclusion reached. As noted above, Dr. Healy has reached his conclusion by conducting [**37] his own so-called Healthy Volunteer Study, using the results of two challenge-dechallenge-rechallenge articles, conducting a Meta-Analysis of Pfizer's own clinical trial data and applying Koch's Postulates to his hypothesis that Zoloft causes suicide. The Court examines whether Dr. Healy's technique in each of these areas constitutes generally accepted methodology.

[*1076]

a. Healthy Volunteer Study

Pfizer argues that Dr. Healy's Healthy Volunteer Study did not adequately test his theory that Zoloft causes suicide because he did not initially provide his methodology or use a placebo control. While Dr. Healy has now provided his methodology, the independent experts concluded that "the healthy volunteer study is not a sufficient basis for calculating any statistically significant relative risk, due to issues involving study design and sample size." n41 They noted that because "the phenomenon of patients reporting symptoms while taking placebo is more the rule than the exception," the study raised a question "what potential information is unavailable due to the absence of a

placebo group" - e.g., would patients receiving placebo have reported any fluctuations in their emotional [**38] state when asked to keep a diary, etc. More importantly, Dr. Concato and Dr. Davis criticized Dr. Healy's methodology because (1) it involved extensive interaction between research personnel and participants; and (2) in the circumstances, statistical calculations represented a statistical "exercise" rather than a statistically significant result. n42 Furthermore, Dr. Healy and his research assistant personally recruited the subjects from the department of which Dr. Healy is the director and each volunteer was "more or less aware" of Dr. Healy's expected outcome. From these criticisms, especially in light of the small sample size, the Court must readily conclude that Dr. Healy's Healthy Volunteer Study does not represent a generally accepted methodology for testing the hypothesis that Zoloft causes suicide.

n41 Independent Expert Report (Doc. # 502) at 17.

n42 Independent Expert Report (Doc. # 502) at 17-18.

b. Challenge-Dechallenge-Rechallenge Reports

In concluding that Zoloft causes [**39] suicide, Dr. Healy relied upon two challenge-dechallenge-rechallenge studies which are basically case reports regarding nine individuals (of approximately 1,542) who developed suicidal ideation or behavior during treatment with fluoxetine (Prozac). According to the independent experts, heavy reliance on case reports is not an accepted methodology for determining the strength of association which Dr. Healy advocates between Zoloft and suicide. n43

n43 Id. at 4.

A major problem is that "suicides would be expected among patients taking sertraline, and the occurrence of such events does not establish causality." n44 It is therefore generally accepted methodology to "control" or "adjust" for factors (such as propensity to commit suicide) that may influence the strength of the cause-effect association. In this context, the independent

experts noted that determining the strength of an association requires at least two groups of subjects, one exposed to the agent of interest (sertraline), the other not so exposed, [**40] so that rates of the outcome event (suicide) can be determined and compared. . . . The lack of a comparison group would . . . make a series of case reports unsuitable for determining the quantitative strength of an association, regardless of other attributes. n45

n44 Id. at 4.

n45 Id. at 4-5.

Also, as Dr. Davis noted at the Daubert hearing, a rechallenge study can consist of merely anecdotal evidence with many possible explanations - including coincidence. n46 Dr. Davis explained.

n46 Transcript (Doc. # 550) at 34-35, 65.

[*1077]

Anecdotal studies are important because the brilliant clinician might discover something that everybody else missed and it might be proven ten years later. . . . So I'm not putting down anecdotal information, but there's a lot of room for coincidence, particularly in patients who were recurrently [**41] suicidal. So could be suicidal one week, okay the next week, suicidal another week. And you could get things occurring by coincidence. So it's hard to take that as definitive proof.

Id.

Dr. Healy's citation of the Rothschild study is particularly problematic because after it was published, the authors issued a letter to the editor which refuted the analysis that Dr. Healy now attempts to draw from their work. n47 They explained that their article did not stand for the proposition that fluoxetine causes suicide, but rather that the development of akathisia (as a side effect of fluoxetine) was one of several factors that led depressed patients to attempt suicide. n48

n47 A.J. Rothschild and C. Locke, Reply, 53 J. Clin. Psychiatry 256-57 (July 1992).

n48 Dr. Rothschild has also signed an affidavit which states that his study did not have a control group, that two of the participants who experienced adverse effects had been nonresponders to other drugs and may have been at a higher risk of suicide regardless of the drug they took, and that his case reports do not causally support an inference that Prozac can lead to suicide because they do not constitute valid scientific evidence on which an opinion regarding causation can be based. See Rothschild Affidavit (Exhibit D) in Reply In Support Of Defendant Pfizer Inc.'s Motion To Exclude The Testimony Of David Healy (Doc. # 536) filed November 1, 2001. Dr. Davis noted that Dr. Rothschild could have withdrawn his conclusion because he "agreed with me that anecdotal information has its limitation and it could be coincidence, and he wanted to make that clear in the affidavit." Transcript (Doc. # 550) at 83-84. On the other hand, he noted that "the drug companies are the major funding of a lot of research, and you never can rule out somebody giving, not wanting to offend a drug company." Id. at 84.

[**42]

[HN5] Use of a small number of challenge-dechallenge studies to test a hypothesis is inadequate and not generally accepted methodology. See Hollander v. Sandoz Pharm. Corp., 95 F. Supp. 2d 1230, 1234 n.10 (W.D. Okla. 2000) (three challenge-dechallenge reports insufficient to be of consequence). The Court finds that cases reports - even those gathered and reported as challenge-dechallenge-rechallenge studies - do not represent a generally accepted methodology for evaluating whether Zoloft causes suicidal behavior in otherwise depressed patients.

c. Meta-Analysis

On April 15, 2000, plaintiffs claimed that through calculations which involved Pfizer's own data, Dr. Healy had confirmed the hypothesis that Zoloft causes suicide. As noted above, according to plaintiffs, his review indicated a "relative risk of suicidal acts

on Zoloft, compared to placebo and corrected for exposure times of 2.19 (i.e. 2.31 vs. 1.0555)." Pfizer questions those calculations and has submitted an affidavit which suggests that they are impossible. Indeed, the independent experts have reported that they cannot replicate Dr. Healy's relative risk calculation of 2.19. n49 Armed with [**43] this information in advance of [*1078] the Daubert hearing, Dr. Healy made some effort to explain and defend his calculation. When discussing the calculation with Dr. Concato, he explained that he had calculated the number based on patients and not patient years. n50 Even with this information, Dr. Concato could not verify the validity of Dr. Healy's calculation. n51 Dr. Concato and Dr. Davis expressed concern about Dr. Healy's calculation and a desire for Dr. Healy to produce more information to validate the number. As the Court explained, however, Dr. Healy's opportunity to declare the bases for his opinion and produce evidence to support it has come and gone. n52 Because the experts cannot replicate Dr. Healy's calculation based on the information that he timely provided and Dr. Healy does not defend it based on that information, the Court has no alternative but to conclude that it does represent generally accepted methodology.

n49 Independent Expert Report (Doc. # 502) at 13. The experts also addressed three exhibits that Dr. Healy had introduced during his deposition on March 27, 2000. See Healy Deposition Testimony And Exhibits (Exhibit 61) in Appendix Of Exhibits (Nos. 52-75) To Defendant Pfizer Inc's Pretrial Motions ("Pfizer's Pretrial Ex. Nos. 52-75") (Doc. # 230). The first two exhibits came from a European meeting on neuropsychopharmacology in 1999.

The data in Exhibit 12 came from a study conducted by Dr. David Baldwin regarding the number of suicide attempts in a double-blind, randomized controlled trial involving placebo and paroxetine, another SSRI. The study apparently spanned a six-month period and revealed that 2.3 patients per thousand on placebo and 7.5 patients per thousand on paroxetine would attempt to commit suicide. Dr. Healy, who created the graph, did not know exactly how many patients were involved in the trial, other than that it was a low number. He believed that this data

showed, however, that SSRI drugs as a class exhibit a propensity to cause suicide.

Exhibit 13 is data from a clinical trial of a French anti-depressant, Milnacipran. The exhibit measures suicide attempts per 100 patient years and found that Milnacipran had roughly 7, tricyclic antidepressants had about 9 and SSRIs had around 22. The Court gathers from Dr. Healy's testimony that the data actually comes from a meta-analysis of other studies.

Exhibit 14, a graph created by Dr. Healy, measures suicide attempts on fluoxetine based on randomized, controlled trial data from Eli Lilly. In trials involving 8,000 patients, Dr. Healy found 2.5 suicide attempts per thousand patients on placebo, 3.8 suicide attempts per thousand patients on tricyclic antidepressants and 12.5 suicide attempts per thousand patients on SSRI drugs. Dr. Healy did not know the time period involved in this study.

The experts found that none of the figures in Exhibits 12, 13 and 14 conformed to generally accepted methodology. They stated that

In particular, the numbers of patients in each group are not reported, and the statistical significance of the results (e.g., shown by "error bars") are not provided. In addition, the Y-axis is not defined for Exhibits 12 and 14. (We reserve judgment and comment on the quality of the "data" itself.)

Independent Expert Report (Doc. # 502) at 16. [**44]

n50 Transcript (Doc. # 552) at 369.

n51 Id. at 371.

n52 Id. at 392.

e. Koch's Postulates

As noted above, Koch's Postulates are a series of factors which are designed to assist in determining general causation and whether a drug may cause a certain reaction. Reference Manual

(1st ed. 1994). Because Dr. Healy's conclusion as to general causation is so heavily dependent on his application of Koch's Postulates, the Court asked its independent experts to evaluate this methodology in particular detail. After completing their review, Dr. Concato and Dr. Davis determined that while some elements of his approach were customary and accepted methods of applying Koch's Postulates, other elements were inconsistent with Koch's Postulates and their application. n53 Overall, because Dr. Healy had focused on the association between SSRI drugs and akathisia - rather than the direct association between SSRI drugs and suicide - the independent experts concluded that Dr. Healy's application of Koch's Postulates was not generally accepted by the scientific community. n54 As [**45] discussed below, they also cited specific deficiencies of Dr. Healy's methodology in applying the postulates.

n53 Independent Expert Report (Doc. # 502) at 1.

n54 Id. at 10.

[*1079]

Strength Of Association

The first postulate concerns the strength of the association between the exposure and effect; it is measured by relative risk. The higher the relative risk, the greater the likelihood that the relationship is causal. n55 See Reference Manual (2nd ed. 2000) at 376. "Relative risk is one of the cornerstones for causal inferences." Id. at 376. As noted above, Dr. Healy concluded with respect to this factor that akathisia is a clear-cut event which is strongly associated with some insult to the central nervous system such as drug intake and, in the case of Zoloft, akathisia may occur in at least a mild form in over 50 per cent of the patients who are taking it. Pfizer challenges Dr. Healy's application of this postulate on two grounds, claiming that Dr. Healy has no scientific evidence [**46] that Zoloft patients are at increased risk of akathisia, and that unless Zoloft creates a relative risk of greater that 2.0, Dr. Healy's testimony is inadmissible.

n55 See In re Breast Implant Litig., 11 F. Supp. 2d 1217, 1226-27 (D. Colo. 1998) (testimony about medical causation only relevant if it shows that conduct of defendant is more likely substantial factor in the plaintiff's injury; must show statistically significant relative risk greater than 2.0); Wade-Greaux v. Whitehall Lab., Inc., 874 F. Supp. 1441, 1452 (D.V.I. 1994) ("A relative risk of '2.00' means that the disease occurs among the exposed population with twice the frequency as the disease occurs among the unexposed population. . . . It means that there is a 50% chance that a particular case of the disease was associated with the exposure and a 50% chance that the disease was not associated with the exposure.").

Preliminarily, the Court rejects Pfizer's argument that unless Zoloft is shown to create a relative [**47] risk greater than 2.0, Dr. Healy's testimony is inadmissible. According to Dr. Concato and Dr. Davis, the magnitude of relative risk is a continuum and a threshold of 2.0 is an arbitrary cut-off. n56 They explained that even strong associations may turn out to be false and that the rigor of the study design and the quality of the data collection are more important than the precise magnitude of the risk. n57 Furthermore, statistical significance - as expressed by confidence intervals, P values or both - is important in determining the stability of a relative risk calculation. n58

n56 Independent Expert Report (Doc. # 502) at 12.

n57 Id. at 12-13.

n58 Id.

The Court recognizes that other courts have adopted a 2.0 relative risk calculation as the benchmark for admissibility of expert testimony. See Allison v. McGhan Med. Corp., 184 F.3d 1300, 1315 n.16 (11th Cir. 1999) (relative risk greater than 2.0 allows inference that agent caused illness; risk of 1.24 insufficient); [**48] Pozefsky v. Baxter Healthcare Corp., 2001 U.S. Dist. LEXIS 11813, No. 92-314 LEKRWS, 2001 WL 967608 (N.D.N.Y. Aug. 16, 2001) (breast implant plaintiff must show relative risk greater than 2.0). On this record, especially in light of the testimony of its independent experts, this Court

declines to do so. See Magistrini v. One Hour Martinizing Dry Cleaning, 180 F. Supp. 2d 584, 2002 U.S. Dist. LEXIS 342, 2002 WL 27318, at *16 (D.N.J. 2002) ("[A] relative risk of 2.0 is not so much a password to a finding of causation as one piece of evidence, among others for the court to consider in determining whether an expert has employed a sound methodology in reaching his or her conclusion."); Pick v. Am. Med. Sys., Inc., 958 F. Supp. 1151, 1160 (E.D. La. 1997) ("A relative risk above 1.0 is statistically significant, even if not sufficient, by itself, to establish causation by a preponderance of the evidence.").

Pfizer also challenges Dr. Healy's application of this postulate on the ground that [*1080] he has no scientific evidence that Zoloft patients are at increased risk of akathisia. The Court need not address this issue in light of its finding - based on the testimony of its independent [**49] experts - that generally accepted methodology in this case required Dr. Healy to consistently test the strength of association between SSRI drugs and suicide (the outcome of interest) - rather than the association between SSRI drugs and akathisia (which is purported to be part of the chain of events that lead to suicide, rather than an independent outcome) or, in other cases, the association between SSRI drugs and improvement in symptoms of depression. n59 Furthermore, as the independent experts explained, determining the strength of association "requires at least two groups of subjects, one exposed to the agent of interest (sertraline), the other not exposed, so that rates of the outcome event (suicide) can be determined and compared," n60

n59 Independent Expert Report (Doc. # 502) at 1, 10.

n60 Id. at 4-5. According to the independent experts, RCTs provide an opportunity to assess whether suicide is more common with one agent as opposed to another, or a placebo, without the threat of susceptibility bias (confounding) affecting the results. Such trials are useful in calculating relative risks, due to the protection randomization provides against confounding bias. Id. at 13. Other types of research design are "less useful." Id. at 16.

[**50]

In concluding that akathisia may occur in at least a mild form in over 50 per cent of the patients who take Zoloft, Dr. Healy reasons as follows: (1) clinical trial data suggest that up to 25 per cent of patients who take Prozac may have "very marked akathisia;" (2) "as a matter of certainty," the method of data collection in clinical trials "significantly under-estimates the extent of the problem;" (3) in the case of SSRI-induced sexual dysfunction, such data collection methods reported an incidence rate of five per cent when the "true incidence is of the order of 50%;" (4) general placebo controlled trials suggest that nervousness and anxiety occur in 10 to 30 per cent of the population taking SSRI drugs; (5) tests by Eli Lilly suggest that such data collection methods "may underestimate the burden of side-effects by a six-fold factor;" and (6) if this applies to "akathisia spectrum effects" in the case of Zoloft, akathisia "may occur in at least a mild form in over 50% of patients taking the drug. This reasoning says nothing about the extent to which nervousness, anxiety and akathisia appear in the population at large - let alone the population of untreated patients with depression [**51] or depressed patients who are treated with non-SSRI drugs." [HN6] Even if Dr. Healy is not legally required to show a relative risk of at least 2.0, he must rely on studies which yield results that are statistically significant regarding the causal relationship at issue in this case. See Magistrini, 180 F. Supp. 2d 584, 2002 U.S. Dist. LEXIS 342, 2002 WL 27318, at *16 (expert's failure to adequately address relative risks weighed in court's conclusion that methodology was unreliable); Siharath v. Sandoz Pharm. Corp., 131 F. Supp. 2d 1347, 1358 (N.D. Ga. Mar. 1, 2001) (expert's failure to derive statistically significant relative risk greater than 2.0 rendered testimony inadmissible). The independent experts were not able to derive statistically significant results from the materials which Dr. Healy provided. For these reasons, the Court must conclude that Dr. Healy did not apply the first of Koch's Postulates in a manner which satisfies Daubert.

Consistency With Other Research

Koch's Postulates ask whether the proposed association is consistent with other research. Reference Manual (2nd ed. 2000) at 379. Dr. Healy does not discuss the fact that other research is contrary to his [**52] conclusion. According to the independent [*1081] experts, his failure to do so constitutes a misapplication of Koch's Postulates - which are "commonly applied in the context of other research, including in this case the consideration that depression itself may have led to suicide." n61 Dr. Healy's misapplication of Koch's Postulates is highly material, given the large body of research from RCTs with placebo controls which refute or fail to support his opinions. n62 Dr. Healy has not directly responded to this fact, other than to attack the drug companies who funded and analyzed the data and disavow the need for RCTs and large scale epidemiological studies. n63 This response in itself is apparently inconsistent with generally accepted methodology, which credits the role of RCTs and large-scale epidemiological studies as "very pertinent" in evaluating the relative risks of potential associations between sertraline and suicide. n64 The Court therefore concludes that in failing to discuss the consistency of his hypothesis with other research, Dr. Healy has not used generally accepted methodology.

n61 Independent Expert Report (Doc. # 502) at 5. [**53]

n62 The independent experts summarize that data, along with observational studies, in their expert report. Id. at 14-15.

n63 See August 13, 2000 Healy Declaration (Exhibit 91) in Pfizer's Pretrial Ex. Nos. 86-99 (Doc. # 232) at 0000083.

n64 Independent Expert Report (Doc. # 502) at 5.

Alternative Explanations

Koch's Postulates provide that to avoid reaching an erroneous conclusion, a scientist should rule out alternative explanations. See Reference Manual (2nd ed. 2000) at 374. Dr. Healy omitted

of Clinical Research Associates; David Dunner, M.D., professor in the Department of Psychiatry, University of Washington; Keh-Ming Lin, M.D., Director of Research on the Psychobiology of Ethnicity at the UCLA Medical Center; Regina Casper, M.D., professor of Psychiatry at the University of Chicago; and Nina Schooler, Ph.D., director of the Psychosis Research Program, Western Psychiatry Institute and Clinic, University of Pittsburgh. Consultants to the committee included Dr. Martin Teicher, whose case reports had given rise to the theory that Prozac caused suicidal behavior; Ida Hellander, M.D., one of the individuals who had signed the Public Citizen Petition; J. John Mann, M.D., professor of Psychiatry at the University of Pittsburgh (now at Columbia University); Stewart Montgomery, M.D., member of the Academic Department of Psychiatry of St. Mary's Hospital; Darrel A. Reiger, M.D., Director of the Division of Clinical Research, National Institute of Mental Health; and Michael Stanley, Ph.D. of Columbia University College of Physicians and Surgeons. Various FDA members (Michael Bernstein, M.P.H., Paul Leber, M.D., Robert Temple, M.D., Thomas Laughren, M.D. and Bruce Stadel, M.D.) also attended and participated. See Bernstein Letter To PDAC Members (Exhibit PP) in Def.'s Failure To Warn Ex., Vol 4 (Doc. # 227). [**39]

n52 See Transcript of Proceedings (Exhibit Z) in Def.'s Failure To Warn App., Vol. 2 (Doc. # 225) at 302.

n53 Id. at 331. The minority of members who voted to change the warnings opined that the change should be for *all* antidepressant drugs; none voted that the change should be limited to SSRI drugs. See PDAC Transcript (Exhibit Z) in Pfizer's Failure To Warn Ex., Vol. 2 (Doc. # 225) at 332:4-18.

n54 Id. at 129:16-19.

Upon reviewing the PDAC report, the FDA determined that while there was no reasonable evidence of a causal relationship between Prozac and suicide, more testing was appropriate. n55 At about the same time, in November of 1991, Dr. J. John Mann,

Healy found that akathisia has a fairly predictable temporal onset in relation to the intake of Zoloft, i.e. 24 to 48 hours following the institution of treatment or an escalation of dose (a phenomenon which [*1082] builds to a peak over one to two weeks as the drug dosage rises in the body).

Pfizer attacks Dr. Healy's application of this postulate because he claims that SSRIs do not begin treating depression for two to three weeks, but that they cause suicide after one or two weeks of therapy. Dr. Davis testified, however, that it is possible for sertraline to produce negative side effects before it begins to work in a beneficial way. n66

n66 Transcript (Doc. # 550) at 46-47.

Pfizer also contends that Dr. Healy [**56] also does not show a temporal relationship between Zoloft ingestion and Zoloft-induced suicide as opposed to *depression*-induced suicide. Pfizer concedes that Matthew Miller ingested Zoloft before he committed suicide, but insists that in order to satisfy this postulate, Dr. Healy must definitively show that Zoloft (as opposed to depression) caused the suicide. Pfizer's position begs the question, however, since a definitive answer to this question would render the other Postulates superfluous. The possibility that something other than Zoloft caused Matthew's suicide is addressed by the postulate concerning alternative explanations, and also by arguments about specific causation. Dr. Healy's proffered testimony satisfies the generally accepted methodology for this postulate.

Biological Plausibility

Under Koch's Postulates, the factor of biological plausibility can be difficult and "depends upon existing knowledge about the mechanisms by which the disease develops." Reference Manual (2nd ed. 2000) at 378. "The saliency of this factor varies depending on the extent of scientific knowledge about the cellular and subcellular mechanisms through which the disease [**57] process works." Id. As to this factor, Dr. Healy stated that there appears to be a "clear biological mechanism" by which SSRI drugs produce akathisia. He does not identify this "clear

biological mechanism," other than to state that it can be "blocked or ameliorated" through other drugs. Pfizer notes that in applying this factor, Dr. Healy connects Zoloft and akathisia rather than Zoloft and suicide, and that his expert reports reveal no discussion that directly connects akathisia (or Zoloft) to suicide.

Dr. Concato and Dr. Davis noted that Dr. Healy's method of determining biological plausibility - that Zoloft leads to akathisia and emotional blunting which in turn causes suicide - may be a suitable explanation *if* there is a relationship between sertraline and suicide. n67 Dr. Healy provided no explanation regarding the biological plausibility of his theory that Sertraline causes *either* akathisia or suicide. His application of this postulate does not constitute generally accepted methodology.

n67 Id. at 1. Although Dr. Davis opined that akathisia is unpleasant and may play a role in suicide, he also expressed concern during the Daubert hearing as to whether emotional blunting could cause suicide. Transcript at (Doc. # 550) 36-37.

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Specificity Of Association

Under Koch's Postulates, specificity of association will be found if exposure to the agent is only associated with a single disease. See Reference Manual (2nd ed. 2000) at 379. Lack of specificity of association does not necessarily undermine the case for causation when there is a biological explanation for its absence. n68 Id. This factor can be helpful, however, in strengthening the case for causation. Id.

n68 Tobacco, for example, is linked with many health hazards and therefore lacks specificity. See Reference Manual (2nd ed. 2000) at 379. The biological explanation for this, however, is that tobacco and cigarette smoke consist of numerous harmful agents and exposure to multiple agents may lead to multiple side effects. Id.

[*1083]

In addressing this factor, Dr. Healy determined that not all antidepressants appear capable of producing akathisia and that "there is . . . greater specificity in the relationship between an SSRI and akathisia than [**59] there is between the SSRI and the response of a depressive disorder." In other words, Dr. Healy admits that not all antidepressants cause akathisia. From the record, it appears that even specific classes of antidepressants (such as SSRI drugs) do not all produce akathisia. In fact, SSRI drugs which may appear to produce akathisia in some patients at certain doses at certain times do not have that effect on other patients. In applying this postulate, Dr. Healy does not pretend to address any association between akathisia and suicide or Zoloft and suicide. The Court must therefore conclude that he has not used generally accepted methodology in addressing this postulate.

Dose-Response Relationship

This postulate addresses that idea that the more intense the exposure to a particular agent, the greater the risk of disease. See Reference Manual (2nd ed. 2000) at 377. Some agents do not exhibit a dose-response relationship when there is a threshold phenomenon (the exposure must exceed a certain dose to produce the disease). See id. Therefore this factor may be helpful, but it is not essential in proving causation. See id. As to dose-response relationship, Dr. [**60] Healy stated that there appears to be a clear dose-response relationship between SSRI intake and akathisic phenomena. Again, however, he does not address a dose-response relationship between SSRI drugs and suicide. In this regard he has not used a generally accepted methodology in his analysis of this postulate.

Additional Factors

In applying Koch's Postulates, Dr. Healy added four factors which Mr. Koch himself did not include: salience of association, consistency of association, support by experiment and support by analogy. In its initial analysis of Dr. Healy's work, the Court was unsure whether these factors have been or currently are part of Koch's Postulates. n69 Dr. Concato and Dr. Davis found that Dr. Healy's additional postulates were unnecessary, however, and

merely repeated information which was addressed in already-existing postulates. n70 Thus, utilizing these postulates does not constitute generally accepted methodology.

n69 The postulates have changed over the years. Certain factors, such as the existence of a dose-response relationship and specificity of the association, are no longer very significant and may not be applicable in some situations, while other factors are sometimes added. See Reference Manual (2nd ed. 2000) at 377, 379; Independent Expert Report (Doc. # 502) at 9-10, compare Reference Manual (1st ed. 1994) with Reference Manual (2nd ed. 2000) (later edition adds replication of findings and cessation of exposure). The independent experts noted that although application of the postulates cannot be simplified to the extent of identifying more important or less important factors for all circumstances, the postulates were not meant to be used in a one-size-fits-all manner and certain factors may be less applicable in certain situations. Independent Expert Report (Doc. # 502) at 9-10. [**61]

n70 Independent Expert Report (Doc. # 502) at 8-9.

As noted above, as to salience of association (which he explained as "the difficulty in otherwise explaining the effect"), Dr. Healy stated that the association between SSRI drugs and akathisia may be "very salient," in that the patient may be visibly distressed and clearly deteriorated "with no . . . means of explaining what is happening other than by invoking an action of a drug." The independent experts noted that in this context, "salience of the association" appears to invoke a criterion of [*1084] "obvious" cause and effect (e.g., an anaesthetic and falling asleep). Koch's Postulates were developed and applied in the context of chronic diseases, however, for which the association of cause and effect was not obvious. As such, this factor per se is not a part of Koch's Postulates. Rather, in a more general sense, the existing postulates (such as temporal association) may be said to address the overall salience of the association.

As to support by experiment, Dr. Healy cited his Healthy Volunteer Study, stating that in his tests, [**62] healthy volunteers who took droperidol became akathisic and up to five became suicidal with two becoming acutely suicidal within hours of treatment. Dr. Healy posits that this experiment constitutes "strong evidence" in favor of the proposed mechanism of action whereby an SSRI drug may produce suicidality. The independent experts explained that "support by experiment" is not a category of Koch's Postulates because experiments generate information for other (existing) postulates but do not constitute postulates unto themselves. Therefore Dr. Healy's approach would tend to provide an indirect and possibly vague endorsement of a proposed cause and effect association.

As to support by analogy, Dr. Healy states that according to case reports, patients on Reserpine (a drug active on the serotonin system which "probably causes akathisia by similar mechanisms to Zoloft") and Prozac (another SSRI drug) committed suicide even though they were "not depressed at all" and had "no nervous condition on which the suicide could be blamed." According to Dr. Healy, these case studies by analogy provide "strong evidence" of a causal relationship between SSRI intake and suicidality. According to the [**63] independent experts, "support by analogy" appears to be a variation on the postulates that address biological plausibility and coherence with existing information, and it does not appear to be necessary. n71

n71 Independent Expert Report (Doc. # 502) at 9.

Finally, Dr. Healy has added a factor called "consistency of association." In applying it, he states that akathisia has a physiological input which appears to occur across all personality types, and akathisia in response to a particular agent strongly predicts renewed akathisia on further exposure to the triggering agent. Given his failure to address the direct linkage between Zoloft and suicide and the overwhelming deficiencies in his application of Koch's Postulates, the addition of this extraneous factor is perhaps best characterized as harmless error. In any event, the Court concludes that it is subsumed in established factors and that it does not constitute any part of a generally accepted methodology for applying Koch's Postulates.

In summary, [**64] Dr. Healy has misapplied, failed to satisfy, or failed to address six of the seven postulates (strength of association, consistency with other research, alternative explanations, biological plausibility, specificity of association and dose-response relationship). To compound this problem, he has invented other factors and variously applied or misapplied them in ways which make it impossible to discern what his conclusions would be if they rested only on generally accepted methodology. Dr. Healy adequately addressed only one of the postulates (temporal relationship). While "there is no formula or algorithm that can be used to assess whether a causal inference is appropriate based on the guidelines," see Reference Manual (2nd ed. 2000) at 375, the Court concludes by overwhelming evidence that Dr. Healy's application of the postulates is not generally accepted methodology. [*1085] In their report the independent experts issued the follow conclusion: n72

n72 Independent Expert Report (Doc. # 502) at 18.

The theory [**65] that sertraline increases the risk of suicide rests largely on case reports of suicide among patients taking sertraline, a posited connection between akathisia (as a side effect of sertraline use) and suicide, and the report of suicidal ideation in two healthy volunteers given sertraline. These "lines of evidence" only partially satisfy Koch's postulates.

In reviewing the Daubert factors, the Court finds that the flaws in Dr. Healy's methodology - particularly his Healthy Volunteer Study, his Meta-Analysis of Pfizer data and his application of Koch's Postulates - are glaring, overwhelming and unexplained, and that his testimony on general causation (which is premised on those methodologies) must therefore be excluded from evidence. Consideration of such evidence would only serve to confuse and mislead the jury and waste the time and resources of the parties and the Court. Plaintiffs concede that Dr. Healy has not cited the Hindmarch Study as a basis for his expert opinion and that they will not cite that study as part of their case in chief on the issue of general causation. That leaves Dr. Healy with a handful of case reports to substantiate his distinctly minority position [**66] that to a reasonable degree of medical

certainty, Zoloft causes otherwise depressed patients to commit suicide. The Court has already determined that heavy reliance on case reports is not an accepted methodology for determining the strength of association between Zoloft and suicide. The Court therefore has no alternative but to sustain Pfizer's motion to prohibit Dr. Healy's testimony on the subject of general causation and to prohibit plaintiffs from using at trial the Hindmarch Study, the Healthy Volunteer Study and the Pfizer Meta-Analysis.

B. Specific Causation

Dr. Healy proposes to testify as to specific causation: that in his opinion, based on a review of notes by Matthew, reports by Matthew's father, and the deposition of Matthew's psychiatrist, Zoloft more likely than not caused Matthew to commit suicide and no other factor in his background or psychosocial situation could explain his suicide. n73 Pfizer argues that Dr. Healy's testimony is not adequate to show specific causation and that at the time of his deposition on March 27, 2000, Dr. Healy had not even bothered to review much of the factual evidence regarding Matthew's symptoms, behavior and social and [**67] family circumstances.

n73 Dr. Healy stated that he had looked at details in Matthew's notes (including a note that Matthew wrote about his feelings regarding the family's move to a new neighborhood), read reports prepared by Matthew's father, and reviewed the deposition of Dr. Douglas Geenens, the psychiatrist who prescribed Zoloft for Matthew. See Exhibit 2 in Plaintiffs' Pretrial Ex., Vol. I (Doc. # 368) at P 13. Dr. Healy contends that suicide is a "vanishingly rare" event for a 13 year-old boy and that no factor beside Zoloft can explain his suicide.

Indeed, Dr. Healy's contention ignores undisputed evidence that Matthew Miller engaged in suicidal thoughts and behavior before he first took Zoloft. Plaintiffs took Matthew to see a psychiatrist because he had been struggling with mood, anger and school-related issues. n74, n75 In a diagnostic [*1086] consultation, Matthew told the psychiatrist that although he would not do it, he had thought about killing himself. n76 On the

second visit with the psychiatrist, [**68] plaintiffs said that even though things were going well, Matthew was still irritable, socially withdrawn, in a low mood, and used profanity. n77

n74 Exhibit 39 in Plaintiffs' Pretrial Ex., Vol. II (Doc. # 369) at 24:12-23, 101-109 (reasons Matthew began seeing Dr. Geenens; Matthew had suspensions for vandalism, bullied other children); see also Exhibit 72 in Pfizer's Pretrial Ex. Nos. 52-75 (Doc. # 230) filed April 18, 2000 (grade cards indicating growing difficulty with school).

n75 On April 28, 2000, plaintiffs moved to exclude hearsay statements in school records or from witnesses about Matthew being violent or suicidal. See Plaintiffs' Motions In Limine Nos. 1-7 And Memorandum And Suggestions In Support Of Plaintiffs' Motions In Limine (Doc. # 246). On September 5, 2001, the Court held a telephone hearing and sustained plaintiffs' motion See Minute Sheet (Doc. # 500). Even so, the Court may still utilize school records that are not hearsay (or are hearsay exceptions) in its ruling. [HN7] Grade cards that schools keep in the ordinary course of business are exceptions to the hearsay rule under Fed. R. Evid. 803(6). See, e.g., Roberts v. Bowersox, 61 F. Supp. 2d 896, 931 (E.D.Mo. 1999) (defendant successfully introduced his school records under business record exception to hearsay). In addition, the information relied upon by Dr. Geenens need not be admissible at trial for the Court to examine the bases for his decision that Matthew's mental state warranted medication. See [HN8] Fed. R. Evid. 703 (bases for opinion testimony need not be admissible). [HN9] Rule 702 mandates that the Court determine the admissibility of expert testimony, but Rule 703 allows for opinion testimony to be based on inadmissible evidence. Logically, whether or not the actual testimony will be admissible at trial, the Court may learn about potentially inadmissible testimony in reviewing the material that the expert did (or did not) base his opinion upon." [**69]

n76 Exhibit 39 in Plaintiffs' Pretrial Ex., Vol. II (Doc. # 369) at 22:1-6.

n77 Id. at 43.

Upon reviewing case material, Dr. Morton Silverman, plaintiffs' expert on suicidology, concluded that based on difficulties with interpersonal relationships, preoccupations with sexual topics, declining school performance and episodes of aggression, Matthew had three risk factors for suicide: diagnosis of depression, being a white male and having a school referral for counseling. n78 In addition, the day before Matthew's death, one of his best male friends had moved; he apparently was Matthew's only male friend in his grade at his new school, and Matthew seemed depressed about the move. n79 The incidence of suicide in Matthew's age group is not - as Dr. Healy would have the Court and the jury believe - "vanishingly rare." Dr. Concato and Dr. Davis cited information from National Alliance for the Mentally Ill that based on 1996 data, suicide is the fourth leading cause of death among ten to 14 year-olds. n80

n78 See Exhibit 66 in Defendant's Exhibits Nos. 52 To 75 (Doc. # 230) at 5. On April 18, 2000, Pfizer moved to exclude the testimony of Dr. Silverman. See Defendant Pfizer Inc.'s Motion To Exclude Opinion Testimony Of Morton M. Silverman (Doc. # 200). On June 26, 2000, the Court issued a Memorandum And Order (Doc. # 200) which sustained in part and overruled in part Pfizer's motion. Specifically, the Court found that Dr. Silverman was qualified to testify regarding the existence of both risk factors and protective factors for suicide. See id. at 5. [**70]

n79 See Exhibit 84 in Defendant's Exhibits Nos. 76 To 85 (Doc. # 231) at 14-16; Exhibit 39 in Plaintiffs' Pretrial Ex., Vol. II (Doc. # 369) at 39-40.

n80 Independent Expert Report (Doc. # 502) at 6.

From the outset, the Court has entertained concerns about the degree of Dr. Healy's reliance on pre-selected evidence from interested parties, to the exclusion of reliable evidence that Matthew engaged in suicidal thoughts and behavior before he first used Zoloft. The Court therefore asked its independent experts whether selective reliance was consistent with generally

accepted methodology on this issue. Their response was predictable and well-founded within the bounds of the case law under Daubert: "the exclusion of evidence [*1087] is not generally accepted practice" because researchers typically evaluate information from relevant sources and consider it when assessing a cause and effect relationship. n81 Stated otherwise, obtaining information from sources that support, refute or are neutral regarding the hypothesis is appropriate to minimize the likelihood of a false conclusion. [**71] n82 Dr. Davis noted that it is difficult to know exactly how much information to explore: n83

n81 Id. at 8.

n82 Id.

n83 Transcript (Doc. # 550) at 76.

It's always a matter of how thorough you want to be. And I don't think there's any black or white. I think if the patient kept a diary of their events, what was in their mental process, that might be very relevant to look at and might be a significant admission. Sometimes if things are very clearcut, there might be an answer. It might be irrelevant to explore all of the odd things. Any avenue you don't explore, people can claim you weren't thorough enough. And the question is how much is enough and I don't know. . . . But I would certainly like to know what was in the patient's mind before the suicide if there was any diary or notes before.

Dr. Healy has given scant attention to evidence to factors - other than Zoloft - which may have caused Matthew's suicide. Dr. Healy's testimony on specific causation does not satisfy Rule 702 because [**72] it does not utilize sufficient facts and data and it is not the product of reliable principles and methods. Moreover, because the Court has sustained Pfizer's motion to preclude Dr. Healy from testifying as to general causation, and Dr. Healy is plaintiffs' only expert on the subject, the issue of specific causation is for all practical purposes moot. The Court therefore finds that Dr. Healy's testimony on the issue of specific causation is inadmissible.

C. Dr. Healy's Areas Of Expertise

Pfizer argues that Dr. Healy may not give testimony on suicidology, warning labels or the FDA regulation of pharmaceuticals because those areas are outside the scope of his expertise. The law is clear that [HN10] "merely possessing a medical degree is not sufficient to permit a physician to testify concerning any medical-related issue." Ralston v. Smith & Nephew Richards, Inc., 275 F.3d 965, 970 (10th Cir. 2001) (orthopedic surgeon and oncologist not qualified to testify regarding warnings on intramedullary nailing device). [HN11] Plaintiffs thus have the burden of establishing the admissibility of Dr. Healy's opinions. Id. at 970 n.4.

1. Suicidology

As [**73] noted above, Dr. Healy is an eminent psychiatrist and neuropsychopharmacologist who has specialized in the areas of depression and psychiatry throughout his career; he has made many important clinical contributions, along with important contributions to the history of psychiatry, and is an accomplished researcher in the area of neuropsychopharmacology. Pfizer nonetheless faults Dr. Healy's expertise with regard to suicidology because Britain does not have a suicidology association and Dr. Healy has only conducted one clinical study in the area. Plaintiffs contend that Dr. Healy is competent to testify about suicide because he has conducted extensive study and publication in the area and his work has clearly touched upon areas which involve suicide or suicidal ideation as a negative outcome (his work involving SSRI drugs in particular). n84

n84 Dr. Healy submitted a declaration that he has proposed a symposium on Psychotropic Drug Associated Suicidality to the British Association for Psychopharmacology and it has been accepted. Exhibit 2 in Plaintiffs' Pretrial Ex., Vol. I (Doc. # 368) at P62. Dr. Healy's more recent work has particularly reflected his interest in the issue of treatment-induced suicide. Id.

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As to suicidology, the Court is not certain what the gist of Dr. Healy's expert testimony would be - especially given the Court's rulings with regard to Dr. Healy's views on general causation and specific causation. Even so, the Court is unimpressed with Pfizer's argument. Rule 702 does not require that Dr. Healy be the preeminent suicidologist in the world, merely that he be able to offer an opinion that will assist the trier of fact, is based upon sufficient facts or data, is the product of reliable principles and methods, and has applied the principles and methods reliably to the facts of the case. Except as to the issues whether Zoloft generally causes suicide and whether Zoloft caused Matthew Miller in particular to commit suicide, Pfizer has not seriously called into question Dr. Healy's expertise on suicidology. Particularly since the Court is not informed what specific opinions Dr. Healy might offer on other points, it declines to determine in advance of trial that Dr. Healy cannot satisfy Rule 702 because he lacks sufficient expertise on the issue of suicide.

2. Warning Labels

Based on his experience as a practicing physician who prescribes Zoloft and [**75] has written extensively about the dangers of SSRI-induced suicide, Dr. Healy proposes to testify that Zoloft labels do not adequately warn against the danger of SSRI-induced suicide. Plaintiffs argue that because he is a practicing physician who prescribes Zoloft and has written extensively about the need for warnings regarding the dangers of SSRI-induced suicide, Dr. Healy is competent to testify that Zoloft warning labels are inadequate. Pfizer contends that Dr. Healy has no experience, training or education that make him an expert in United States prescription drug warnings and that he cannot say what specific words would make a warning adequate.

As an initial matter, the fact that Dr. Healy prescribes SSRI drugs and studies whether they tend to induce suicidal ideation and behavior does not necessarily render him an expert on the adequacy of warnings for SSRI drugs. In Ralston, 275 F.3d at 970, the Tenth Circuit held that an orthopedic surgeon and oncologist was not qualified to testify about warnings

concerning an intramedullary nailing device - a device designed to hold together pieces of fractured bones. Plaintiff alleged that the manufacturer had not properly [**76] warned her treating physician that one of its devices was more durable than another. Her expert was not allowed to testify that the warnings were inadequate, however, because although she dealt with the devices, her real area of expertise was bone healing and oncology. Id. at 969. In affirming the district court, the Tenth Circuit held that [HN12] the dispositive question is whether the adequacy of the warning is within the reasonable confines of the expert's subject area. Id. at 970. There, the expert had not researched the device or published articles about it, and had never drafted or been asked to draft a surgical technique or warning of any kind. Id. The Tenth Circuit noted that [HN13] "whether or not a given warning is adequate depends upon the language used and the impression that it is calculated to make upon the mind of an average user of the product." See Robertson v. Norton Co., 148 F.3d 905, 907 (8th Cir. 1998) (citations omitted) (ceramics expert who could testify about manufacturing defect not qualified to testify about warning since it involved "questions of display, syntax, and emphasis"). Perhaps Dr. Healy can supply helpful [**77] testimony in this [*1089] limited area, by explaining what effect a given warning might communicate to an average physician, but he cannot testify as to the ultimate issue and opine that the warnings were inadequate as a matter of his expert opinion and that he could design a better warning. See id. (error to admit opinion testimony on ultimate issue of fact that warnings were "completely inadequate" when expert was not qualified in area of warnings).

The issue is complicated, however, by the fact that the Court has already determined that Dr. Healy will not be allowed to testify that Zoloft causes akathisia, which in turn causes suicide in depressed patients. The Court is therefore somewhat at a loss to determine what expert testimony Dr. Healy might offer on the subject of warnings. If the jury will hear no evidence that Zoloft causes suicide, it cannot possibly conclude that Zoloft labels do not adequately warn against the danger that Zoloft causes suicide. Therefore, even if Dr. Healy could supply helpful testimony in the limited area of explaining what effect a given

warning might communicate to an average physician, that testimony would essentially be irrelevant to any larger [**78] issue in the case.

Furthermore, Dr. Healy's admits that he "would not hold himself up as the world authority as to just what wording should be put in, but I do not believe that the warnings were adequate." n85 Dr. Healy did propose four definitions of akathisia that he believed would have been reasonable to include in a Zoloft label. n86 When asked if anything else would suffice, however, Dr. Healy testified that you would need an expert in - obviously companies hire legal experts in when they're constructing the labeling to work out the legal implications of what they put in. You would ideally need - if you are going to do an educational job with the labeling, that you would ideally need someone who was an educator in public communication to work out what the best words would be; and working from the kind of materials that I have offered you, I will be happy with whatever words such person came up with. n87

n85 See Exhibit 61 in Pfizer's Pretrial Ex. Nos. 52 To 75 (Doc. # 230) at 314-42.

n86 Id.

n87 Id. at 347:12-22.

[**79]

Dr. Healy has not drafted any sort of proposed warning; without any data or research regarding their potential efficacy, he has merely offered phrases that he thinks might be reasonably included. This fact weighs heavily against a finding that Dr. Healy is a qualified warnings expert. See Bourelle v. Crown Equipment Corp., 220 F.3d 532, 539 (7th Cir. 2000) (failure to draft proposed alternative warning renders opinion inadmissible; opinion merely "talking off the cuff"); Jaurequi v. Carter Mfg. Co., Inc., 173 F.3d 1076, 1084 (8th Cir. 1999) (failure to design warning, much less test its effectiveness rendered proffered expert testimony inadmissible; proximate cause also problematic on different grounds); Milanowicz v. The Raymond Corp., 148

F. Supp. 2d 525, 541 (D.N.J. 2001) [HN14] (reliability of expert testimony extremely questionable when he failed to design and test proposed warning and could not point to contrary industry practice).

While plaintiffs claim that Dr. Healy has written extensively on the subject of warnings, the cited articles do not necessarily lead to that conclusion. The first two articles mention warnings in [**80] passing, but they do not reveal that Dr. Healy possesses any particular expertise on the topic. n88 The third article is actually a guest editorial [*1090] which posits that pharmaceutical companies avoid posting warnings by relying on physicians to tell their patients the risks of the drugs, but it likewise reveals no special expertise in the area of warnings. n89 Ultimately, plaintiffs do not meet their burden of showing that Dr. Healy possesses knowledge that would allow him to opine on the subject of warnings. Thus his testimony on the matter of warnings is inadmissible.

n88 D. Healy, et al., Suicide In The Course Of The Treatment Of Depression, 13 J. Of Psychopharmacology 1, 94-99 (1999), and D. Healy and A. Boardman, Suicide Risk In Affective Disorders. Time To Revise Our Estimates?, (submitted for publication), The first article alludes to warnings in mentioning that "there is an increasing onus on prescribers and companies to acquaint themselves with the hazards of treatment, to inform the patient on how to handle these [side effects] and to monitor the impact of treatment." The second article focuses on whether the lifetime prevalence rate for suicide in affective disorders is an overestimate and does not appear to directly address warnings at all. [**81]

n89 D. Healy, A Failure To Warn, 12 Int't J. Of Risk & Safety 151-56 (1999).

3. FDA Regulations

Finally, based on his familiarity with the American regulatory system, Dr. Healy proposes to testify about FDA regulation of SSRI drugs in general and sertraline in particular. As with his testimony about suicidology, the precise scope and content of his proposed testimony is unclear. Plaintiffs argue that even though Dr. Healy practices in the United Kingdom, he is very familiar with the American regulatory system and can testify regarding the FDA regulation of SSRI drugs in general and sertraline in particular. Specifically, Dr. Healy has written a book that discusses FDA regulations; n90 published interviews with Dr. Paul Leber, the former FDA chief regulator for psychoactive drugs; and in his role as secretary of the British Association of Psychopharmacology, organized and hosted an educational program which involved regulators from all over the world. While other individuals might have more specific expertise than Dr. Healy in the area of FDA regulations, Pfizer has not [**82] seriously called into question the fact that he does have expertise and experience which might assist the jury in evaluating the evidence before it. Particularly since the Court is not informed what specific opinions Dr. Healy might offer in this area, it declines to determine in advance of trial that Dr. Healy cannot satisfy Rule 702 because he lacks sufficient expertise on the issue of FDA regulations which would enable him to offer admissible opinions on that subject.

n90 The Antidepressant Era (1998).

II. Plaintiff's Post Hearing Memorandum, And Request For Independent Expert Verification (Doc. # 545)

Plaintiffs ask that the Court order the independent experts to evaluate and verify a relative risk calculation from data available in the Myers Report. The Myers Report summarizes the sertraline safety data that Pfizer prepared for the PDAC of the FDA and submitted on September 14, 1990. Plaintiffs argue that Pfizer tendered this exhibit after the experts had left the Daubert hearing and [**83] that the calculation which they request would yield a relative risk calculation of 3.01 for Zoloft, relative

to placebo. n91 Pfizer asserts that [*1091] plaintiffs and Dr. Healy had the Myers Report for three years before the hearing, that Dr. Healy relied on it in his declaration of May 9, 2000, that it was provided to the independent experts, and that Dr. Healy and the independent experts testified about it at length during the Daubert hearing in this case. When he formulated his expert opinions in this case, however, Dr. Healy did not make a relative risk calculation using that data. Pfizer argues that now - long after Dr. Healy's numerous expert reports, Dr. Healy's deposition, scrutiny of Dr. Healy's methodology by the independent experts and a two-day Daubert hearing - plaintiffs want to bootstrap into the record entirely new calculations of relative risk. Pfizer asks the Court to deny plaintiffs' request.

n91 In part, plaintiffs complain that Pfizer massaged its data by calculating it in terms of patient years and not on a per patient basis. Numbers based on a patient year analysis might be artificially low since a patient who committed suicide soon after beginning treatment would not contribute that many years to the study, as compared to a patient who successfully took Zoloft for a number of years. The Court notes, however, that the experts had access to the Ryder Report, a 1992 Pfizer document that discusses suicide attempts and ideation in the sertraline depression treatment program, which analyzes the data per patient and not per patient year. Transcript (Doc. # 550) at 74.

[**84]

However else plaintiffs may have obtained a copy of the Myers Report, the Court notes that it is contained in defendant's exhibits to pretrial motions which it filed April 18, 2000. n92 Plaintiffs presumably received a copy of these exhibits, including the Myers Report. Plaintiffs have previously argued that Pfizer inundated them with paper, making it difficult to separate the wheat from the chaff. In this instance, however, Pfizer relied on the report in its pretrial motions. Even though it filed 99 exhibits with its motions, plaintiffs cannot argue that the report was buried in the bottom of a box or hidden in a cavernous storage area. Any calculations that they and Dr. Healy wanted to make from this report could - and should - have been

made *well before* this point in the litigation. Although the record is not entirely clear on this point, Dr. Healy's Meta-Analysis apparently relied on information from the Myers Report, as well as data from unspecified sources. The parties also submitted the Myers Report to the independent experts. As noted earlier, the independent experts have already tried to perform the very calculations that plaintiffs seek, and they report that they [**85] cannot verify Dr. Healy's calculations from the data in the report. n93 Finally, Dr. Healy's testimony has been a moving target throughout this litigation and, as Pfizer notes, the Court tried to curtail *further* movement during the Daubert hearing by repeatedly telling plaintiffs' counsel that

n92 See Exhibit 12 in Appendix Of Exhibits (Nos. 1-25) To Defendant Pfizer Inc's Pretrial Motions ("Pfizer's Pretrial Ex. Nos. 1-25") (Doc. # 228) filed April 18, 2000.

n93 Transcript (Doc. # 550) at 70-71.

Dr. Healy's testimony would be limited to the reports and affidavits which he has previously submitted and which were made available to the Court's experts. The one exception to that would be with regard to scientific developments that occurred after the time that the record was put together in this case and information that the Court's experts either might have taken into account or that Dr. Healy might have taken into account that was not available to him at the time of the original expert [**86] reports. Outside of the scope of that exception would be information which was available to him that was available to [plaintiffs] but [they] just didn't send to him or information which he had but chose not to use at that time. n94

n94 Transcript (Doc. # 551) at 213:9-24.

Plaintiffs' counsel admitted that the graphs and calculations which he sought to introduce were not based on new scientific developments or new information from the experts. The Court therefore finds that Pfizer's opposition to plaintiffs' motion has merit. Therefore, although it is not prepared to give plaintiffs an award for creative ways of avoiding the Court's ruling as to the scope of the evidence it would consider [*1092] at the Daubert

hearing, it also is not prepared to sanction them for over-zealous advocacy. The Court therefore overrules plaintiffs' request for independent expert verification of the figures they request.

III. Motion For Sanctions Against Dr. Healy (Doc. # 534)

Pfizer asks the Court to sanction [**87] Dr. Healy for violating the protective order in this case. n95 During the Daubert hearing, the Court heard oral argument and evidence on this motion. As a sanction for violation of the protective order in this matter, Pfizer urges the Court to disqualify Dr. Healy as a witness. In its motion, Pfizer also asks the Court to (1) preclude plaintiffs from using the Hindmarch study at trial, (2) direct plaintiffs and their counsel to identify all other protected materials that Dr. Healy has disclosed, (3) direct plaintiffs and their counsel to retrieve all copies and notes of protected materials from Dr. Healy, (4) seal the declaration of Dr. Healy which is attached to plaintiff's supplemental response to the Court's show cause order (Doc. # 458) filed September 11, 2000, and (5) award costs and fees associated with the motion. On November 20, 2001, however, counsel for Pfizer told the Court that "if Your Honor grants our Daubert motion, then that will take care of the matter." n96 Although the Court has already determined that defendant's Daubert motion should be granted in part and that Dr. Healy's testimony not admitted on the subjects of general causation, specific causation [**88] and warnings, it is not prepared to entirely exclude Dr. Healy's testimony based on Daubert. The Court will therefore analyze the merit of Pfizer's motion.

n95 See Minute Sheet (Doc. # 91) filed December 16, 1999 (motion for protective order sustained).

n96 Transcript (Doc. # 552) filed on November 30, 2001 at 474:9-11.

The protective order states that "confidential information shall not be used or shown, disseminated, copied, or in any way communicated, orally or verbally, to anyone for any purpose whatsoever, other than as required for the preparation and trial of this action." n97 During the course of discovery, Pfizer produced to plaintiffs an unpublished document by Dr. Ian

Hindmarch titled A Double-Blind, Placebo-Controlled, Cross-Over Study To Assess The Effects Of Sertraline, Alone And With Diazepam, On Psychomoter Performance. The so-called Hindmarch Study involved healthy volunteers who had been given sertraline. The study had to be aborted, however, because of a mini-revolt [**89] among the subjects - who felt that they could not function on sertraline. Pfizer contends that Dr. Healy violated the protective order by disclosing the existence of the Hindmarch study in two letters to the Medicines Control Agency ("MCA"), the British counterpart to the FDA, dated August 3, 2000 and September 1, 2000. On October 11, 2000. Dr. Healy's letter was discussed in a British publication, in an unsigned article titled *MCA Wants SSRI Suicide Warning*, Scrip: World Pharm. News at 2-3 (Oct. 11, 2000). The article stated as follows:

n97 Protective Order (Doc. # 81) file December 17, 1999 at P4.

In his letter, Dr. Healy highlighted two studies showing that healthy volunteers exhibited signs of suicidal thoughts after takings SSRIs. One of these studies was performed by Professor Ian Hindmarch, the other by Dr. Healy himself.

The Hindmarch study was performed about 10 years ago in the UK and was sponsored by Pfizer. The study looked at Pfizer's sertraline, but has never been [*1093] published, and [**90] as it was strictly confidential Dr. Healy said he could not provide *Scrip* with further details. However, he did claim that the MCA has seen the study, but consider that the number of volunteers in it was too small to show any conclusive results.

Plaintiffs contend that Dr. Healy only divulged information which he had learned from conversations with Dr. Hindmarch before he received the confidential document in this case, and that he did not divulge information gleaned from confidential documents in this case. Specifically, Dr. Healy testified that he saw Dr. Hindmarch at a meeting in Prague in 1998 and mentioned an article in the New Yorker in which the author compared the effects of Zoloft to drinking 55 cups of black coffee. Dr. Hindmarch allegedly expressed interest in the article

and mentioned that his interest stemmed from a similar experience with patients in a healthy volunteer study that he had conducted (the Hindmarch Study). After his own Healthy Volunteer Study in 1999, Dr. Healy called Dr. Hindmarch to get more information about the Hindmarch study. Dr. Healy claims that Dr. Hindmarch then divulged all of the details that Dr. Healy later mentioned in his letter [**91] to the MCA. n98

n98 Plaintiffs also point out that although Dr. Healy and defense counsel discussed the Hindmarch Study at length during Dr. Healy's deposition, the deposition has not been sealed or marked confidential and it is therefore a matter of public record. In addition, plaintiffs assert that defense counsel "virtually invited" Dr. Healy to share his concerns with a regulatory body; that Dr. Healy shared only what he learned from Dr. Hindmarch himself; that Dr. Healy shared his information in a way that demonstrated his knowledge that the Hindmarch Study results were confidential; and that after he sent the letter, Dr. Healy learned that the MCA already had a copy of the allegedly confidential study.

Dr. Hindmarch testified that in Prague, in 1998, he in fact discussed the black coffee article and a Zoloft study with Dr. Healy. Dr. Hindmarch testified, however, that he was referring to a *different* Zoloft study - one which was published. Dr. Hindmarch did not remember discussing the unpublished [**92] study and in his conversation with Dr. Healy in Prague, he may or may not have stated that he was discussing a published study. Dr. Hindmarch also testified that Dr. Healy called him at his home after he had completed his own Healthy Volunteer Study, and asked for information regarding Dr. Hindmarch's study. Dr. Hindmarch assumed that Dr. Healy was referring to the unpublished study (which had been aborted). He was surprised that Dr. Healy knew about the study and told Dr. Healy that he was well informed. Dr. Hindmarch then gave Dr. Healy details about the study. At some period after this conversation, Dr. Healy received the Hindmarch Study from Pfizer with the confidential designation.

Pfizer first argues that two declarations by Dr. Healy prove that he only learned of the confidential study from Pfizer documents.

The first declaration, dated August 31, 2000, swore that "had I been aware of the Hindmarch study before conducting my study, the situation would have been different and certainly would have given me food for thought. I would have raised the possibility with the healthy volunteers but, in point of fact, the possibility of them becoming suicidal was not mentioned to [**93] any of them." According to Pfizer, this declaration shows that (1) Dr. Healy would have told his healthy volunteers about the Hindmarch Study (and the possibility of suicide) if he had known about the study in 1999, when he did his study; (2) Dr. Healy did not so warn his volunteers; (3) therefore, Dr. Healy must have learned about the Hindmarch Study through confidential documents in this case - and not, as he claims, in Prague in 1998. On the other [*1094] hand, the second declaration, dated October 30, 2000, swore that Dr. Healy first learned of Dr. Hindmarch's healthy volunteer study in 1998 - before his own Healthy Volunteer Study.

Although Pfizer's explanation is plausible, Dr. Healy's testimony at the hearing shows that these statements are reconcilable. Dr. Healy's testimony was that before his own Healthy Volunteer Study, he knew that Dr. Hindmarch had conducted a healthy volunteer study that involved patients having reactions akin to drinking 55 cups of coffee. After his own study was done, but before he received Pfizer's confidential document, Dr. Healy learned details about Dr. Hindmarch's work which suggested that patients believed they could not function on Zoloft.

Pfizer [**94] also contends that Dr. Healy's deposition testimony shows that he did not learn of the Hindmarch Study until he received the confidential documents from Pfizer. The Court has reviewed this deposition testimony. None of it conclusively support Pfizer's position.

Ultimately, Pfizer has produced no evidence which rebuts the admission by Dr. Hindmarch that he told Dr. Healy the details of the Hindmarch Study in late 1999 or early 2000 and the testimony by Dr. Healy that this conversation took place before he received the confidential documents in this case. For this reason, the Court cannot find that Dr. Healy violated the Court's protective order.

IT IS THEREFORE ORDERED that the Court adopts the Report Of Independent Experts (Doc. # 502) filed September 5, 2001.

IT IS FURTHER ORDERED that Defendant Pfizer's Inc's Refiled Motions To Exclude The Testimony Of Dr. David Healy And For Sanctions Against Dr. David Healy For Violations Of The Court's Protective Order (Doc. # 534) filed November 1, 2001 be and hereby are **SUSTAINED in part**. The Court will exclude Dr. Healy from testifying about (1) general causation (whether Zoloft causes suicide); (2) [**95] specific causation (whether Zoloft caused Matthew Miller's suicide); and (3) the adequacy of Pfizer's Zoloft warnings to physicians. The Court **OVERRULES** Pfizer's motion in part as to testimony regarding suicidology and the FDA's regulation of pharmaceuticals.

IT IS FURTHER ORDERED that Defendant Pfizer Inc's Motion In Limine No. 9 To Exclude The Use At Trial Of The Hindmarch Study, Dr. Healy's "Healthy Volunteer Study," And Dr. Healy's Statistical Analysis Of The Pfizer Meta-Analysis (Doc. # 304B) filed April 28, 2000 be and hereby is **SUSTAINED.**

IT IS FURTHER ORDERED that Defendant Pfizer Inc.'s Opposition To Plaintiffs' Post-Hearing Memorandum And Request For Independent Expert Verification; Request For Sanctions (Doc. # 547) filed November 29, 2001 be and hereby is **SUSTAINED** in its opposition to the request for independent expert verification of the Myers Report and **OVERRULED** as to its request for sanctions.

IT IS FURTHER ORDERED that Plaintiff's Post-Hearing Memorandum, And Request For Independent Expert Verification (Doc. # 545) filed November 27, 2001 be and hereby is **OVERRULED.**

IT IS FURTHER ORDERED that [**96] the Clerk of the Court send copies of this Memorandum and Order to the Court-appointed experts, in addition to counsel of record:

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University of Illinois at Chicago

Department of Psychiatry

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New Haven, CT 06510.

Dated this 7th day of February, 2002 at Kansas City, Kansas.

Kathryn H. Vratil

United States District Judge

LEXSEE 196 F. SUPP. 2D 1095

MARK MILLER AND CHERYL MILLER, INDIVIDUALLY AND MARK MILLER AS ADMINISTRATOR OF THE ESTATE OF MATTHEW MILLER, DECEASED, Plaintiffs, v. PFIZER INC (ROERIG DIVISION), Defendant.

CIVIL ACTION No. 99-2326-KHV

UNITED STATES DISTRICT COURT FOR THE DISTRICT OF KANSAS

196 F. Supp. 2d 1095; 2002 U.S. Dist. LEXIS 2388; CCH Prod. Liab. Rep. P16,293

February 11, 2002, Decided

SUBSEQUENT HISTORY: Affirmed by, Motion to strike granted by, Motion denied by Miller v. Pfizer, Inc., 2004 U.S. App. LEXIS 1711 (10th Cir. Kan., Feb. 4, 2004)

DISPOSITION: [**1] Defendant's partial summary judgment motions on both of plaintiffs' claims granted and motion in limine overruled as moot. Plaintiffs' motion for partial summary judgment overruled. Defendant's motion in limine to exclude references to its financial condition and announced merger overruled as moot.

CASE SUMMARY:

PROCEDURAL POSTURE: Plaintiff parents filed suit against defendant drug manufacturer, claiming the manufacturer was strictly liable for marketing defects and misrepresentations about a prescription antidepressant, and liable under common law negligence theories for failing to test and warn about the dangers of drug-induced suicide. Both parties moved for partial summary judgment.

OVERVIEW: The parents claimed that their 13-year-old son committed suicide because he took the antidepressant. The treating physician stated he was aware of possible adverse

reactions to the drug, would not have read warnings whether or not they had been given, and would have prescribed the drug regardless of warnings. Because the parents did not specifically identify a particular theory of fraudulent misrepresentation or explain any alleged marketing defect, the court construed their first count strictly as a fraud count. So construed, the allegations failed to satisfy pleading requirements. Moreover, the parents cited no evidence of any "great lengths" to which the manufacturer went to assure doctors that violence and suicide problems would not occur with the drug. The parents also presented no evidence that the treating physician relied on marketing influences that were fraudulent. It appeared the parents' position rested only on the hope that a jury would refuse to believe the treating physician. The parents also failed to meet their burden of proving medical causation since they failed to present testimony that the drug more likely than not caused the son's suicide.

OUTCOME: The court granted both of the manufacturer's motions for summary judgment and overruled the motion in limine as moot.

LexisNexis (TM) HEADNOTES - Core Concepts:

Civil Procedure > Summary Judgment > Summary Judgment Standard

[HN1] Summary judgment is appropriate if the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any, show no genuine issue as to any material fact and that the moving party is entitled to a judgment as a matter of law. Fed. R. Civ. P. 56(c). A factual dispute is "material" only if it might affect the outcome of the suit under the governing law. A "genuine" factual dispute requires more than a mere scintilla of evidence.

Civil Procedure > Summary Judgment > Burdens of Production & Proof

[HN2] On a motion for summary judgment, the moving party bears the initial burden of showing the absence of any genuine issue of material fact. Once the moving party meets its burden,

the burden shifts to the nonmoving party to demonstrate that genuine issues remain for trial as to those dispositive matters for which it carries the burden of proof. The nonmoving party may not rest on its pleadings but must set forth specific facts.

Civil Procedure > Summary Judgment > Summary Judgment Standard

[HN3] On a motion for summary judgment, the court must view the record in a light most favorable to the parties opposing the motion for summary judgment. Summary judgment may be granted if the non-moving party's evidence is merely colorable or is not significantly probative. In a response to a motion for summary judgment, a party cannot rely on ignorance of facts, on speculation, or on suspicion, and may not escape summary judgment in the mere hope that something will turn up at trial. Essentially, the inquiry is whether the evidence presents a sufficient disagreement to require submission to the jury or whether it is so one-sided that one party must prevail as a matter of law.

Civil Procedure > Summary Judgment > Supporting Papers & Affidavits Civil Procedure > Summary Judgment > Burdens of Production & Proof

[HN4] Under U.S. Dist. Ct., D. Kan., Rule 56.1(b)(1), on a motion for summary judgment, the party opposing facts shall refer with particularity to those portions of the record upon which the opposing party relies.

Civil Procedure > Summary Judgment > Burdens of Production & Proof

[HN5] Under U.S. Dist. Ct., D. Kan., Rule 56.1(a), those material facts which plaintiffs have failed to adequately controvert are deemed admitted for purposes of summary judgment.

Governments > Agriculture & Food > Federal Food, Drug & Cosmetic Act

[HN6] The Federal Food Drug and Cosmetic Act ("FDCA") requires that prescription medicines be approved as safe and effective before they may be sold. 21 U.S.C.S. § 355. The first step to obtain approval for a new prescription drug is to file an

investigational new drug application ("IND"). 21 C.F.R. § 312.2. An IND is filed with the Food and Drug Administration (FDA) after animal and laboratory studies have been completed. 21 C.F.R. § § 312.20, 312.21. The IND describes in detail the product, the studies which have been performed, and a proposed plan for clinical trials with human volunteers. 21 C.F.R. § 312.21-312.22. If the FDA approves the IND, clinical trials may proceed. 21 C.F.R. § 312.20. If the clinical trials and other studies set forth in the IND are successfully completed, a new drug application ("NDA") may be filed with the FDA. 21 C.F.R. § 314. The NDA provides detailed safety and efficacy information about the medicine to the FDA. 21 C.F.R. § 314.50.

Governments > Agriculture & Food > Federal Food, Drug & Cosmetic Act

[HN7] Under the Federal Food Drug and Cosmetic Act, a prescription medication is one which is not safe for use except under the supervision of a practitioner licensed by law to administer such drugs. 21 U.S.C.S. § 353(b).

Governments > Agriculture & Food > Federal Food, Drug & Cosmetic Act

[HN8] The Food and Drug Administration (FDA) must reject a new drug application for particular use if it does not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; the results of such tests show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; or the labeling is false or misleading in any particular. 21 U.S.C.S. § 355(d). To approve a new drug, the FDA must determine that it meets statutory standards for safety and effectiveness and labeling. 21 U.S.C.S. § 355(d). FDA standards provide that a new drug may not be approved for marketing unless is has been shown to be safe and effective for its identified uses. 21 C.F.R. § 310.303(a).

Governments > Agriculture & Food > Federal Food, Drug & Cosmetic Act

[HN9] The Federal Food, Drug, and Cosmetics Act directs the Food and Drug Administration to establish expert panels for the purpose of providing expert scientific advice and recommendations regarding a clinical investigation of a drug or the approval for marketing of a drug. 21 U.S.C.S. § 355(n)(1). The statute requires that such panels consist of: (A) members who are qualified by training and expertise to evaluate the safety and effectiveness of the drugs to be referred to the panel and who, to the extent feasible, possess skill and expertise in the development, manufacture, or utilization of such drugs; (B) members with diverse expertise in such fields as clinical and administrative medicine, pharmacy, pharmacology, pharmacoeconomics, biological and physical sciences, and other related professions; (C) a representative of consumer interests, and a representative of interests of the drug manufacturing industry not directly affected by the matter to be brought before the panel; and (D) two or more members who are specialists or have other expertise in the particular disease or condition for which the drug under review is proposed to be indicated. 21 U.S.C.S. § 355(n)(3).

Governments > Agriculture & Food > Federal Food, Drug & Cosmetic Act

[HN10] The Food and Drug Administration specifically permits doctors to prescribe drugs for off-label uses, i.e. uses for which they have not been approved. 21 U.S.C.S. § 396.

Governments > Agriculture & Food > Federal Food, Drug & Cosmetic Act

[HN11] See 21 U.S.C.S. § 396.

Governments > Agriculture & Food > Federal Food, Drug & Cosmetic Act

[HN12] Under 21 C.F.R. § 201.57(e), labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug, and a causal relationship need not have been proved.

Governments > Agriculture & Food > Federal Food, Drug & Cosmetic Act

[HN13] Labeling requirements adopted pursuant to the Federal Food, Drug, and Cosmetics Act do not prohibit a manufacturer, packer, relabeler, or distributor from warning health care professionals whenever possibly harmful adverse effects associated with the use of the drug are discovered. The addition to labeling and advertising of additional warnings, as well as contraindications, adverse reactions, and precautions regarding the drugs, or the issuance of letters directed to health care professionals (e.g. 'Dear Doctor' letters containing such information) is not prohibited by these regulations.

Torts > Products Liability

[HN14] In Kansas, product liability claims are governed by the Kansas Products Liability Act (KPLA), Kan. Stat. Ann. § 60-3301 et seq. The purpose of the KPLA is to consolidate all product liability actions, regardless of theory, into one theory of legal liability. Under Kan. Stat. Ann. § 60- 3302(c), all legal theories of recovery, e.g., negligence, strict liability, and failure to warn, are to be merged into one legal theory called a product liability claim. KPLA provisions apply to actions based on strict liability as well as negligence, breach of express or implied warranty, and breach of or failure to discharge duty to warn or instruct.

Torts > Business & Employment Torts > Deceit & Fraud Torts > Business & Employment Torts > Negligent Misrepresentation

[HN15] To sustain an action for fraud or misrepresentation in Kansas, plaintiffs must establish among other things that they reasonably relied and acted on the allegedly false representations to their detriment.

Torts > Products Liability

[HN16] In Kansas, the ultimate determination in a products liability case remains whether the product is defective and dangerous beyond a reasonable consumer's expectations.

Torts > Business & Employment Torts > Negligent Misrepresentation

[HN17] In Kansas, the reliance element of misrepresentation serves the function of causation in fact: that the misrepresentation causes someone to act or refrain from acting. For plaintiffs to recover for misrepresentation under Kansas law, they must show reliance.

Torts > Intentional Torts > Defenses Torts > Products Liability > Duty to Warn

[HN18] Under the learned intermediary doctrine, a prescription drug manufacturer's duty to warn is satisfied when the prescribing doctor is informed of a drug's inherent risks. According to the Kansas Supreme Court, the rule is based upon the theory that the physician acts as a learned intermediary between the drug manufacturer and the patient. Because prescription drugs are available only to a physician, it is the physician's duty to inform himself or herself of the characteristics of the drugs prescribed and to exercise his or her judgment of which drug to administer in light of the drug's propensities and the patient's susceptibilities. The learned intermediary doctrine allows the manufacturer to assume a patient places reliance on the physician's judgment and relieves the manufacturer of a duty to assist the physician in communicating with patients. In analyzing whether a warning is sufficiently adequate to inform the treating physician, a court must determine whether the warning is 'reasonable under the circumstances.

Torts > Intentional Torts > Defenses Torts > Products Liability > Duty to Warn

[HN19] Since 1981, when Kan. Stat. Ann. § 60-3305 was enacted, Kansas courts have repeatedly applied the learned intermediary rule.

Civil Procedure > Summary Judgment > Summary Judgment Standard

[HN20] Plaintiffs' hope that something may turn up at trial, or that the jury will disbelieve a witness, is insufficient to survive summary judgment. Where plaintiffs have failed to turn up substantial evidence in support of their theory, and defendants

introduce evidence negating the plaintiffs' theory, it is unreasonable to assume that trial would provide the plaintiffs with any greater opportunity to prove their theory, especially when the most that can be hoped for is to discredit the defendants' witnesses at trial.

Civil Procedure > Summary Judgment > Summary Judgment Standard Torts > Products Liability

[HN21] In a products liability case against a prescription drug manufacturer, summary judgment is appropriate when plaintiffs present no evidence that treating physicians were misled by seminars or promotions or that they relied on the drug manufacturer's representations to the plaintiffs' detriment.

Torts > Products Liability > Duty to Warn

[HN22] In Kansas, manufacturers do not have a duty to test for inconceivable dangers, nor do they have a duty to test for every conceivable danger. They do have a duty to warn of dangers of harmful effects arising from the foreseeable use and misuse of a product that are known or are readily foreseeable in the state of art. Any obligation to test is part of the duty to act in manner reasonably necessary to secure the production of a safe product.

Torts > Products Liability

[HN23] Under Kansas law, regardless of the theory upon which recovery is sought for injury in a products liability case, proof that a product defect caused the injury is a prerequisite to recovery.

Torts > Causation > Proximate Cause Torts > Products Liability > Duty to Warn

[HN24] In order to survive summary judgment in a failure to warn products liability case, plaintiffs must provide evidence that a failure to warn proximately caused the injury.

Torts > Causation > Proximate Cause Torts > Products Liability > Duty to Warn

[HN25] Kansas law allows a rebuttable presumption of causation once plaintiffs in a failure to warn products liability case have established that a warning is inadequate. If plaintiffs prove that the defendant failed to provide a proper warning,

Kansas law presumes that a doctor would have heeded a proper warning. Essentially, the law presumes that but for the inadequate warning, the patient would not have been harmed, since the doctor would have given the patient an adequate warning if she or he had ever received it, and the inadequate warning is therefore the cause of the patient's injury. The defendant may rebut this presumption by establishing that although the prescribing physician would have read and heeded the warning or additional information, this would not have changed his or her course of treatment. If the defendant provides credible evidence to rebut the presumption, the presumption disappears and the burden shifts back to plaintiffs to affirmatively prove causation.

Evidence > Procedural Considerations > Inferences & Presumptions

[HN26] Kan. Stat. Ann. § 60-414 does establish two kinds of presumptions, those that permanently shift the burden of proof when plaintiff has put forth facts that have any probative value as evidence of the existence of the presumed fact, and those that disappear if the facts from which the presumption arises have no probative value as evidence of the presumed fact.

Torts > Products Liability > Duty to Warn

[HN27] A showing that an alleged failure to warn was the proximate cause of a plaintiff's injuries requires that the plaintiff demonstrate that the additional non-disclosed risk was sufficiently high that it would have changed the treating physician's decision to prescribe the product for the plaintiff.

Torts > Causation > Proximate Cause Torts > Products Liability > Duty to Warn

[HN28] In a failure to warn products liability case, where learned intermediary has actual knowledge of substance of alleged warning and would have taken same course of action even with information plaintiff contends should have been provided, courts typically conclude that learned intermediary doctrine applies or that causal link is broken and plaintiff cannot recover.

Governments > Agriculture & Food > Federal Food, Drug & Cosmetic Act
[HN29] When the Food and Drug Administration (FDA) discovers special problems, particularly those that may lead to death or serious injury, it may require a drug manufacturer to place a warning about that problem in a prominently displayed box. 21 C.F.R. § 201.57(e). If a boxed warning is required, the FDA will specify its location.

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JUDGES: Kathryn H. Vratil, United States District Judge.

OPINION BY: Kathryn H. Vratil

OPINION: [*1097]
MEMORANDUM AND ORDER

Mark and Cheryl Miller claim that their 13-year-old son Matthew committed suicide because he took Zoloft - a prescription drug which Pfizer Inc. manufactured for treatment of depression. See Amended Complaint (Doc. # 92) filed December 16, 1999. The Millers seek to hold Pfizer liable for Matthew's wrongful death. Count I of their complaint alleges that Pfizer is strictly liable for marketing defects and misrepresentations about Zoloft. Count II alleges that Pfizer is liable under common law negligence theories for failing to test

and warn about the dangers of drug-induced suicide. See Pretrial Order (Doc. # 171) filed March 6, 2000.

The matter comes before the Court on three motions for summary judgment: Defendant Pfizer Inc's Motion For Partial Summary Judgment On Plaintiffs' Claim Of Marketing Defect And Misrepresentation (Doc. # 505) and Defendant Pfizer Inc's Motion For Partial Summary Judgment On Plaintiffs' Failure To Warn Claim (Doc. # 504), both filed September 12, 2001, and Plaintiffs' Motion For Partial [**3] Summary Judgment (Doc. # 523) filed October 23, 2001. This matter also comes before the Court on Defendant Pfizer Inc.'s Motion In Limine No. 15 To Exclude References To Its Financial Condition And Announced Merger (Doc. # 276) filed April 28, 2000. The Court has carefully considered the parties' arguments and is now prepared to rule.

Summary Judgment Standard

[HN1] Summary judgment is appropriate if the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any, show no genuine issue as to any material fact and that the moving party is entitled to a judgment as a matter of law. Fed. R. Civ. P. 56(c); accord Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 247, 91 L. Ed. 2d 202, 106 S. Ct. 2505 (1986); Vitkus v. Beatrice Co., 11 F.3d 1535, 1538-39 (10th Cir. 1993). A factual dispute is "material" only if it "might affect the outcome of the suit under the governing law." Anderson, 477 U.S. at 248. A "genuine" factual dispute requires more than a mere scintilla of evidence. Id. at 252.

[HN2] The moving party bears the initial burden of showing the absence [**4] of any genuine issue of material fact. Celotex Corp. v. Catrett, 477 U.S. 317, 323, 91 L. Ed. 2d 265, 106 S. Ct. 2548 (1986); Hicks v. City of Watonga, 942 F.2d 737, 743 (10th Cir. 1991). Once the moving party meets its burden, the burden shifts to the nonmoving party to demonstrate that genuine issues remain for trial "as to those dispositive matters for which it carries the burden of proof." Applied Genetics Int'l, Inc. v. First Affiliated Sec., Inc., 912 F.2d 1238, 1241 (10th Cir. 1990); see

also Matsushita Elec. Indus. Co., Ltd. v. Zenith Radio Corp., 475 U.S. 574, 586-87, 89 L. Ed. 2d 538, 106 S. Ct. 1348 (1986); Bacchus Indus., Inc. v. Arvin Indus., Inc., 939 F.2d 887, 891 (10th Cir. 1991). The nonmoving party may not rest on its pleadings but must set forth specific facts. Applied Genetics, 912 F.2d at 1241.
[*1098]

" [HN3] We must view the record in a light most favorable to the parties opposing the motion for summary judgment." Deepwater Invs., Ltd. v. Jackson Hole Ski Corp., 938 F.2d 1105, 1110 (10th Cir. 1991). Summary judgment may be granted if the non-moving party's [**5] evidence is merely colorable or is not significantly probative. See Anderson, 477 U.S. at 250-51. "In a response to a motion for summary judgment, a party cannot rely on ignorance of facts, on speculation, or on suspicion, and may not escape summary judgment in the mere hope that something will turn up at trial." Conaway v. Smith, 853 F.2d 789, 794 (10th Cir. 1988). Essentially, the inquiry is "whether the evidence presents a sufficient disagreement to require submission to the jury or whether it is so one-sided that one party must prevail as a matter of law." Anderson, 477 U.S. at 251-52.

Statement Of Uncontroverted Facts

For purposes of summary judgment, the following facts are uncontroverted, deemed admitted, or, where disputed, viewed in the light most favorable to plaintiffs. n1

n1 [HN4] Under D. Kan. Rule 56.1(b)(1), the party opposing facts "shall refer with particularity to those portions of the record upon which the opposing party relies." In opposing Pfizer's statement of material facts in this case, however, plaintiffs have not consistently cited portions of the record. See, e.g., Statement Regarding Uncontested Material Facts in Plaintiffs' Brief In Support Of Responses To Pfizer's Motion For Summary Judgment On Failure To Warn And Failure To Test Theories (Doc. # 342) filed May 12, 2000, and Plaintiffs' Brief In Support Of Responses to Pfizer's Motions For Summary Judgment On Failure To Warn, And Failure To Test Theories

(Doc. # 515) filed October 3, 2001. Furthermore, many of plaintiffs' factual responses are misnumbered and do not even roughly correspond with the factual statement which they purport to controvert. Therefore the Court cannot understand plaintiffs' factual position. [HN5] Under D. Kan. Rule 56.1(a), those material facts which plaintiffs have failed to adequately controvert are deemed admitted for purposes of summary judgment.

[**6]
. Matthew Miller

In the spring of 1997, staff members at Harmony Middle School (including teachers, school counselors and the school psychologist) were concerned about Matthew Miller. n2 Matthew had expressed suicidal ideation to both Roxanna Rogers, his special education classroom teacher, and his friends (Abby Meckna, Hillary Burton and Chad Brownell). n3 At least two students [*1099] had told Ms. Rogers that Matthew had spoken of suicide. The staff therefore recommended that Matthew's parents seek professional evaluation and treatment for him, and that he see someone for counseling over the summer. Matthew's parents, Mark and Cheryl Miller, were also concerned. On June 30, 1997, they took Matthew to see Dr. Douglas Geenens, who was board certified in psychiatry by the American Board of Psychiatry and Neurology and board certified in child and adolescent psychiatry by the American Board of Psychiatry and Neurology. Dr. Geenens had done a residency in psychiatry at the Menninger Clinic and received further training in child psychiatry at Harvard Medical School. Eighty per cent of Dr. Geenens' practice involved the treatment of children and adolescents.

n2 Roxana Rogers, a special education teacher, testified that Matthew's name had come up in discussions about students with behavioral problems at school. Deposition of Roxana Rogers (Exhibit I) at 12:11-15, 21:5-17. Elizabeth Price, another teacher, testified that at the end of the school year she was very concerned about Matthew. Deposition of Elizabeth Price (Exhibit J) at 76:8-21. Price testified that Matthew could be mean to other classmates and sometimes isolated himself from

other students. Id. at 24:5-24. Lisa Sonsthagen, a certified school psychologist, testified that during the school year Matthew's behavior grew more concerning. Deposition of Lisa Sonsthagen (Exhibit K) at 25:3-26. Becky Loomis, a school counselor, testified that she had increasing concerns about Matthew's academic progress, conduct, emotional state and behavior during the spring of 1997. Deposition of Becky Loomis (Exhibit L) at 14:2-7, 14:14-20. Robert Kreifels, school principal, testified that school officials became concerned about Matthew due to disciplinary issues and bullying behavior. Deposition of Robert Kreifels (Exhibit M) at 14:4-16:14.

All of the referenced depositions are contained in Appendix Vol.2 Defendant's Partial Summary Judgment On Plaintiffs' Failure To Warn Claim ("Def.'s Failure To Warn App., Vol 2") (Doc. # 225) filed April 18, 2000. [**7]

n3 See Rogers Deposition (Exhibit I) at 88:17-89:7, 120:19-121:7, 186:9-21; Loomis Deposition (Exhibit L) at 24:1-25:1-7; Kriefels Deposition at 31:10-32:23; Deposition of Hilary Burton (Exhibit O) at 58:8-61:18; Deposition of Abby Meckna (Exhibit P) at 13:13-14:10, 27:3-31:6, 39:2-21, all in Def.'s Failure To Warn App., Vol 2 (Doc. # 225).

During Matthew's first visit, on June 30, 1997, Dr. Geenens diagnosed Matthew as suffering from "depression not otherwise specified." n4 Three weeks later, on July 21, 1997, Dr. Geenens saw Matthew a second time. At that time, based upon additional tests and further psychiatric evaluation, he concluded that Matthew was significantly depressed and prescribed Zoloft 50 mg. once a day. n5 At the time, Dr. Geenens warned Matthew and his parents that nausea and insomnia were common side effects of Zoloft, and told them to report any problems or anything unusual that happened while Matthew was taking Zoloft. n6 In allowing Matthew to use Zoloft, plaintiffs relied solely on Dr. Geenens' advice. In prescribing Zoloft, Dr. Geenens relied [**8] solely on his education, training, review of medical and scientific literature, the Physician's Desk Reference and his own clinical experience. n7 Dr. [*1100] Geenens testified that he does not review pharmaceutical marketing materials and, when he receives marketing,

advertising or promotional materials from pharmaceutical representatives, he throws them away without reading them. n8 He also testified that he did not read marketing, advertising or promotional materials about drugs in scientific and medical articles or journals. n9 Finally, Dr. Geenens testified that Pfizer sales representatives have never encouraged him to prescribe Zoloft in conditions which the FDA has not approved, and that he knows more about Zoloft than Pfizer sales representatives. See id. at 59-60. In short, Dr. Geenens testified that Pfizer's marketing efforts had no effect on his decision to prescribe Zoloft for Matthew. n10

n4 Plaintiffs deny that Dr. Geenens told them of this diagnosis but they cite no record support for that contention, and they do not deny that Dr. Geenens made that diagnosis.

n5 Plaintiffs claim that the test results were lost and that a jury may not believe that Dr. Geenens performed them. They cite no record evidence for this claim and the Court disregards it. Plaintiffs also claim that Dr. Geenens gave Matthew promotional samples of Zoloft which contained no package inserts. This purported fact is not contained in plaintiffs' statement of undisputed facts, either in support of their own motion or in opposition to Pfizer's motion. In the body of Plaintiffs' Brief In Support Of Response To Pfizer Motion For Summary Judgment On Marketing Misrepresentation ("Plaintiffs' Misrepresentation Response") (Doc. # 516) filed October 3, 2001, plaintiffs cite a portion of Mark Miller's deposition testimony to support their contention that the promotional samples did not have package inserts. See id. at 10 n.2 (citing Exhibit 77 in Appendix Of Exhibits (Nos. 76 To 85) To Defendant Pfizer Inc.'s Pretrial Motions ("Def.'s Pretrial Ex. Nos. 76-85") (Doc. # 231) filed April 18, 2000 at 78-79). The cited pages support plaintiffs' contention that Dr. Geenens gave them promotional samples, but not that those samples did not contain package inserts. The Court will therefore disregard that "fact." [**9]

n6 Deposition of Douglas Geenens (Exhibit D) in Appendix Vol.1 Defendant's Partial Summary Judgment On Plaintiffs' Failure To Warn Claim ("Def.'s Failure To Warn

App., Vol 1") (Doc. # 225) filed April 18, 2000 at 123:18-125:8. Plaintiffs deny that Dr. Geenens told them to report "anything unusual" but they cite no record evidence in support of this denial and the Court disregards it.

n7 See Geenens Affidavit (Exhibit F) in Appendix Defendant's Partial Summary Judgment On Plaintiffs' Claim Of Marketing Defect And Misrepresentation ("Pfizer's Marketing Defect Appendix") (Doc. # 212) filed April 18, 2000 at P2. Plaintiffs claim that in deciding to proscribe Zoloft, Dr. Geenens was heavily influenced by promotional activities by Pfizer. Specifically, plaintiffs argue that "although Dr. Geenens may well think that he has not been influenced by Pfizer's subtle marketing maneuvers, . . . there is a evidence that Pfizer intended from the launch of Zoloft forward to influence physicians' prescribing practices in subtle ways which even they could not discern, . . . and (b) that their efforts succeeded with Douglas Geenens, D.O." Plaintiffs' Misrepresentation Response (Doc. # 516) at 5.

In support of this argument, plaintiffs cite statements by James Lee Jung, the worldwide director of Pfizer's Central Nervous System division. Specifically, plaintiffs cite a speech which Jung gave to professional medical representatives (Pfizer employees who directly communicate drug information to physicians) when Pfizer launched its Zoloft product. Jung advised the representatives to communicate information about Zoloft to high-prescribing physicians and told them not to discuss suicide unless a physician asked about it. Jung told them that if asked, the representatives should say that Zoloft had a low risk of suicidal ideation. He did not want the representatives to bring up the topic because various reports had linked suicide with Prozac (an antidepressant which competed with Zoloft) and physicians could react negatively to an implicit comparison of the two drugs - feeling that Pfizer was unfairly taking advantage of the speculation about Prozac. See Deposition of James Lee Jung (Exhibit 36) in Index Of Plaintiffs' Consolidated Exhibits To Pretrial Motions, Vol. II ("Plaintiffs' Pretrial Ex., Vol. II") (Doc. # 369) filed May 12, 2000 at 91-92, 105-115; Jung Zoloft Launch Speech (Exhibit 48) in Plaintiffs' Pretrial Ex., Vol. II (Doc. # 369).

Unbeknownst to plaintiffs, Dr. Geenens had a pre-existing relationship with Pfizer. For two years, he had received compensation for his speech-making activities on behalf of Zoloft. Also, either shortly before or shortly after Matthew's death, Pfizer hired Dr. Geenens as a consultant to its Central Nervous System Division, which has primary responsibility for Zoloft. See Deposition of Douglas Geenens (Exhibit D) in Def.'s Failure To Warn App., Vol 1 (Doc. # 224) at 68, 128. Through the deposition testimony of Cheryl Miller, plaintiffs also imply that Dr. Geenens was biased. The Court is unclear, however, on what plaintiffs believe that Cheryl Miller's testimony proves. She testified that Dr. Geenens told her that "Zoloft was newer [than Prozac]" and "did not carry the baggage that Prozac had acquired." Cheryl Miller Deposition (Exhibit 70) in Pfizer's Pretrial Ex., Nos. 52-74 (Doc. # 230) at 232. Plaintiffs apparently believe that this evidence can defeat the "learned intermediary" doctrine as it is applied in Kansas. As discussed in the Court's analysis, however, such evidence does not raise a genuine issue of material fact whether, in ways he could not detect, subtle promotional activities by Pfizer caused Dr. Geenens to prescribe Zoloft for Matthew Miller on July 21, 1997. [**10]

n8 See Geenens Deposition (Exhibit G) in Pfizer's Marketing Defect Appendix (Doc. # 212) at 79, 178:1-8.

n9 See id. at 178-79.

n10 See Geenens Affidavit (Exhibit F) in Pfizer's Marketing Defect Appendix at PP2-3; see also Geenens Affidavit (Exhibit N) in Exhibits Vol. 2 Pfizer Inc.'s Opposition In Response To Plaintiffs' Motion For Partial Summary Judgment ("Pfizer's Opposition Ex., Vol. 2") (Doc. # 354b) filed May 12, 2000 at P 9. Plaintiffs object to Dr. Geenens' "POST-DEPOSITION *EX PARTE* AFFIDAVIT," but cite no factual basis for their objection and no legal reason why the Court should not consider it.

At the time he prescribed Zoloft for Matthew, Dr. Geenens knew that published case reports and adverse event reports at the Food and Drug Administration ("FDA") had described instances in

which patients who were undergoing treatment with antidepressants like Zoloft experienced suicidal ideation and committed suicide, or attempted to do so, while undergoing such treatment. In fact, Dr. Geenens was medically trained by Dr. Martin [*1101] Teicher, the principal [**11] author of anecdotal case reports which involved suicidal ideation of patients on Prozac, an antidepressant drug which is similar to Zoloft. In his opinion, however, Zoloft was a safe and effective medication for the treatment of depression. n11 In retrospect, even in the face of plaintiff's evidence Dr. Geenens would have given the Millers the same warning he gave them before concerning Zoloft. n12

n11 Plaintiffs claim that Dr. Geenens testified at his deposition that he would heed any warning from Pfizer. In doing so they misrepresent his actual testimony. Dr. Geenens testified that

Q. You would heed any warning that the drug manufacturer gave you about the risks of their drug, wouldn't you?

A. I would consider that in my clinical decision-making.

Q. Well, can you give me any circumstance in which you in your clinical decision-making would ignore a bold-faced warning in the package insert for a psychoactive drug?

. . .

A. Bold print black box is information that I would incorporate into my clinical decision-making.

Q. Dr. Geenens, I won't quibble with you. I just want to know if there is any circumstance you can envision where you would ignore or fail to heed a bold-faced warning about a drug?

. . .

A. I would do my best to heed that type of warning.

Geenens Deposition (Exhibit 1) in Index to Exhibits To Plaintiffs' Consolidated Statement Of Facts In Support Of Plaintiffs' Motion For Partial Summary Judgment, Vol. I ("Plaintiffs' Ex., Vol. I") (Doc. # 525) filed October 23, 2001 at 89-91. While this may show that Dr. Geenens would incorporate the bold print black box warning into his decision-making, his testimony does not indicate that he would act solely based on that information. In addition, Dr. Geenens' testimony does not refer to a particular warning and on this record, it is insufficient to raise a genuine issue of material fact whether - had he received additional warnings from Pfizer - he would have opted not to prescribe Zoloft. [**12]

n12 See Geenens Affidavit (Exhibit N) in Pfizer's Opposition Ex., Vol. 2 (Doc. # 354b) at P 12.

Plaintiffs did not contact Dr. Geenens about any side effects and to his knowledge, Matthew did not experience any clinically-significant side effects while he was taking Zoloft. Nonetheless, about six days after his second visit with Dr. Geenens, during the late night of July 27 or the early morning of July 28, 1997, Matthew died from asphyxiation. n13

n13 For purposes of this order, the Court assumes that Matthew intended to commit suicide. This issue is contested but it is not material to the motions now pending.

. Regulatory Approval Process For Zoloft

[HN6] The Federal Food Drug and Cosmetic Act ("FDCA") requires that prescription medicines be approved as safe and effective before they may be sold. n14 The first step to obtain approval for a new prescription drug is to file an investigational new drug application [**13] ("IND"). n15 An IND is filed with the Food and Drug Administration after animal and laboratory studies have been completed. n16 The IND describes in detail the product, the studies which have been performed, and a proposed plan for clinical trials with human volunteers. n17 If the FDA approves the IND, clinical trials may proceed. n18 If the [*1102] clinical trials and other studies set forth in the IND are successfully completed, a new drug application ("NDA")

may be filed with the FDA. n19 The NDA provides detailed safety and efficacy information about the medicine to the FDA. n20

n14 **See 21 U.S.C. § 355.** [HN7] A prescription medication is one which "is not safe for use except under the supervision of a practitioner licensed by law to administer such drugs." **21 U.S.C. § 353(b).**

n15 **See 21 C.F.R. § 312.2.**

n16 **See 21 C.F.R. § § 312.20, 312.21.**

n17 **See 21 C.F.R. § 312.21-312.22.**

n18 **See 21 C.F.R. § 312.20.**

n19 **See 21 C.F.R. § 314.** [**14]

n20 **See 21 C.F.R. § 314.50.**

[HN8] The FDA must reject a NDA for particular use if it "does not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; . . . the results of such tests show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; . . . or . . . [the] labeling is false or misleading in any particular." n21 To approve a new drug, the FDA must determine that it meets statutory standards for safety and effectiveness and labeling. n22 FDA standards provide that "[a] new drug may not be approved for marketing unless is has been shown to be safe and effective for its identified uses." n23

n21 **21 U.S.C. § 355(d).**

n22 **21 U.S.C. § 355(d); see also 21 C.F.R. § 314.105(c).**

n23 **21 C.F.R. § 310.303(a)**. Plaintiffs cite testimony by Dr. Paul Leber, who served as Director of the FDA's Division of Neuropharmacological Drug Products and later became Commissioner of the FDA, for the proposition that FDA practice and standards for new drug approval are different from those stated in the governing statutes and regulations. Plaintiffs, however, do not provide a page cite for the comments within the 130-page document that allegedly supports this statement. See PDAC Meeting Transcript (Exhibit 14) Appendix Of Exhibits (Nos. 1-25) To Defendant Pfizer Inc.'s Pretrial Motions ("Def.'s Pretrial Ex. Nos. 1-25") (Doc. # 228). The Court has nonetheless reviewed this document. Apparently plaintiffs are concerned about Dr. Leber's statement that the ideal is never attained in the real world of testing and that Pfizer's studies were "terrible." This does not mean, however, that the FDA would approve drugs that appeared unsafe and ineffective.

[**15]

On October 2, 1980, Pfizer filed an IND for sertraline for use in the treatment of depression. Sertraline is the generic name for Zoloft. n24 The FDA approved the IND, and physicians thereafter conducted clinical trials at 150 clinical centers over a period of several years. On April 13, 1988, Pfizer filed its NDA. The initial submission comprised 117 volumes of scientific information regarding the safety and efficacy of sertraline, as developed in laboratory and clinical testing programs.

n24 See Physician's Desk Reference (54th ed. 2000) at 2399.

[HN9] The FDCA directs the FDA to establish expert panels "for the purpose of providing expert scientific advice and recommendations . . . regarding a clinical investigation of a drug or the approval for marketing of a drug." n25 The statute requires that such panels consist of:

(A) members who are qualified by training and expertise to evaluate the safety and effectiveness of the drugs to be referred to the panel and who, to the extent feasible, possess [**16] skill

and expertise in the development, manufacture, or utilization of such drugs;

(B) members with diverse expertise in such fields as clinical and administrative medicine, pharmacy, pharmacology, pharmacoeconomics, biological and physical sciences, and other related professions;

(C) a representative of consumer interests, and a representative of interests of the drug manufacturing industry not directly affected by the matter to be brought before the panel; and
[*1103]
(D) two or more members who are specialists or have other expertise in the particular disease or condition for which the drug under review is proposed to be indicated. n26

n25 **21 U.S.C. § 355(n)(1).**

n26 **21 U.S.C. § 355(n)(3).**

On September 14, 1990, Pfizer submitted to the FDA a summary report of sertraline safety data for the Psychopharmacological Drugs Advisory Committee ("PDAC"), a summary report of sertraline clinical pharmacology, and a report on sertraline suicide attempts. Pfizer [**17] also submitted HAM-D Suicide Item No. 3, a portion of the Hamilton Depression Rating Scale which measured suicidal depression in the sertraline depression program, and a report on specific HAM-D scores in one clinical study of Zoloft. While the HAM-D has been found to be an insensitive barometer of treatment-emergent suicidality, the data demonstrated that sertraline was more effective than placebo and comparable to active controls with respect to rates of suicide attempts and changes in the depression rating scale item that related to suicide. In particular, the data showed that suicide attempts occurred no more frequently in Zoloft patients (0.3%) than in placebo patients (0.3%). n27 These studies were not designed to detect or measure treatment-emergent suicidality. n28 The FDA reviewed the data from the HAM-D study, and in fact reported it in the Summary Basis of Approval when it later approved Pfizer's NDA for Zoloft. n29

n27 Id.

n28 In his article in 1991, Dr. J. John Mann, professor of Psychiatry at the University of Pittsburgh (now at Columbia University), recommended that instead of the single item HAM-D item 3 scale which Pfizer and Ely Lilly had used in clinical trials for Zoloft and Prozac, future clinical trials or tests employ the more refined Beck's suicidal ideation scale to measure treatment emergent suicidality. See Mann Deposition (Exhibit 3) in Plaintiffs' Ex., Vol. I (Doc. # 525) at 70-71, 80-81. At his deposition Dr. Mann explained that in a sufficiently large sample, the HAM-D item 3 scale is a simpler, less expensive instrument which is sufficient to detect any causal effect between drug therapy and attempted or completed suicides. He explained that in tests which involve fewer subjects, a more sensitive instrument is needed to give an answer that is statistically meaningful, and that this may be accomplished by a more sensitive measurement of suicidal *ideation* - Beck's suicidal ideation scale. Other researchers have opined that the HAM-D is insufficient. See Jonathan Cole Declaration (Exhibit 3) in Plaintiffs' Pretrial Ex., Vol. I (Doc. # 368) at 4; David Healy Declaration (Exhibit 2) in id. at P45 (FDA database of clinical trials is "sadly unreliable"). Pfizer representatives, however, consider the HAM-D scale "an excellent scale." Pfizer does not use the Beck scale to measure suicidal ideation. Harrison Deposition (Exhibit 18) in Plaintiffs' Ex., Vol. I (Doc. # 525) at 61:23-62:4. Even Dr. Mann admitted that the HAM-D has value and that "you can always come up with a better measure." Mann Deposition (Exhibit 3) in id. at 143-44. [**18]

n29 See Summary Basis of Approval (Exhibit EE) in Appendix Vol.3 Defendant's Partial Summary Judgment On Plaintiffs' Failure To Warn Claim ("Def.'s Failure To Warn App., Vol 3") (Doc. # 226) at 38-39.

On November 19, 1990, the FDA convened the 33rd meeting of the PDAC for the sole purpose of reviewing Pfizer's NDA for Zoloft. n30 At the meeting, James F. Knudson, M.D. presented safety data [*1104] (including suicide attempts during clinical studies for Zoloft) on behalf of the FDA. In doing so, he noted that "disproportionate numbers of suicide attempts do not occur

among the 3 treatment groups [Zoloft, placebo and active control]," and that "all suicide attempts appeared in depressed patients, none in the obese [a separate patient population in which Zoloft had been studied]." n31

n30 Participants in the meeting included PDAC Chairman Daniel E. Casey, M.D., a psychiatrist on staff at Portland Veterans Administration Medical Center and Oregon Health Sciences University; representatives of the FDA Neuropharmacological Drugs Division (Paul Leber, M.D. and Thomas P. Laughren, M.D.); Dr. Robert F. Prien, Director of Clinical Psychopharmacology at the National Institute of Mental Health; Dr. Robert M. Hammer, professor of psychiatry and statistics at the Medical College of Virginia; Carol A. Tamminga, M.D., professor of psychiatry at the University of Maryland; Dr. Linda F. Hezel, professor of nursing at the University of Missouri in Kansas City; Jeffrey A. Lieberman, M.D. of Long Island Jewish Medical Center and Albert Einstein College of Medicine; John M. Davis, M.D. of the Illinois State Psychiatric Institute; and Javier I. Escobar, M.D., professor of psychiatry at the University of Connecticut. At the meeting, various FDA representatives, including Dr. J. Hillary Lee, Dr. Ed Nevius, Dr. Japobrata Choudhury and James F. Knudson, M.D. presented safety and efficacy data. On behalf of Pfizer, Steven Ryder, M.D., presented scientific data on safety, efficacy and clinical pharmacology. [**19]

n31 PDAC Transcript (Exhibit 14) in Pfizer's Pretrial Ex. Nos. 1-25 (Doc. # 228) at 30.

At the conclusion of the PDAC meeting, the Committee determined (by a vote of six to one) that there was sufficient evidence that sertraline was effective for the treatment of depression. It also determined (unanimously) that there was sufficient evidence that sertraline was safe for the treatment of depression. n32 At the meeting, however, Dr. Thomas Laughren (a senior FDA official) cautioned that "we have no data for this drug in children . . . . I think it is important to point out that depression is an entity that exists in children and if this drug were to be approved, it is likely that some clinicians will want to use this drug in children." n33

n32 Id. at 116-17.
n33 Id. at 62.

By letter dated September 30, 1991, the FDA informed Pfizer that Zoloft was "approvable." A determination that a medication [**20] is "approvable" means that the FDA will approve the application if specific additional information material is submitted or specific conditions are met. n34 To its letter, the FDA attached a proposal for Zoloft labeling, stating "we believe it presents a fair summary of the information available on the benefits and risks of sertraline." n35 The proposed labeling included the following precaution regarding the risk of suicide in patients undergoing Zoloft therapy:

n34 **21 C.F.R. § 314.3(b)**.

n35 See FDA Letter (Exhibit U) in Def.'s Failure To Warn App., Vol. 2 (Doc. # 225).

Suicide - The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for Zoloft (sertraline) should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

The FDA's proposed [**21] label also included the following statement under the "adverse reactions" heading:

Psychiatric Disorders - Infrequent: abnormal dreams, aggressive reaction, amnesia, apathy, delusion, depersonalization, depression, aggravated depression, emotional lability, euphoria, hallucination, neurosis, paranoid reaction, suicide attempt, teeth-grinding, abnormal thinking; Rare: hysteria, somnambulism, withdrawal symptom.

On October 30, 1991, Pfizer responded to the FDA with a suggestion that the word "capsules" be changed to "tablets," and that the "Psychiatric" subsection of the "Adverse Reactions" section be revised to include suicide "ideation" in addition to

suicide "attempt." n36 Pfizer did not propose other changes to the suicide warning.

n36 CSO Labeling Review (Exhibit JJ) in Appendix Vol.4 Defendant's Partial Summary Judgment On Plaintiffs' Failure To Warn Claim ("Def.'s Failure To Warn App., Vol 4") (Doc. # 227) filed April 18, 2000 at 1, 3-4.

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On December 6, 1991, the FDA completed its review [**22] of the proposed package insert which would contain the Zoloft labeling and it accepted Pfizer's recommendations.

By letter dated December 30, 1991, the FDA approved Pfizer's NDA for Zoloft. In doing so it stated:

We have completed our review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling dated October 30, 1991, as revised below. Additionally, we refer to the December 5, 1991, teleconference between staff from FDA and Pfizer during which agreement was reached on final labeling revisions. Accordingly, the application, with these labeling revisions, is approved, effective as of the date of this letter. n37

n37 See Temple Letter (Exhibit V) in Def.'s Failure To Warn App., Vol. 2 (Doc. # 225).

The FDA also stated: "These revisions [to the label] are terms of the NDA approval. Marketing the product before making the agreed upon revisions in [**23] the product's labeling may render the product misbranded and an unapproved new drug." n38

n38 Id. Since 1992, the FDA has authorized Pfizer to market Zoloft not just for treatment of depression but also for treatment of obsessive compulsive disorder, pediatric obsessive compulsive disorder, panic and post-traumatic stress disorder.

On each occasion, the FDA found that Zoloft was safe and effective for the additional use. In the approval process for each such indication, the FDA reviewed the Zoloft package insert, made changes to it, and approved it with indicated changes.

The FDA has never approved Zoloft for treatment of pediatric depression. At the same time, [HN10] the FDA specifically permits doctors to prescribe drugs for off-label uses, i.e. uses for which they have not been approved. n39 At his deposition, Dr. Geenens testified that "in child psychiatry we prescribe outside of FDA indication 99 percent of the time. It is the standard of care to utilize psychiatric medication in children and extrapolate [**24] from adult literature." n40 Indeed, the FDA's approval letter of December 30, 1991 recommended that Pfizer conduct studies with depressed children and adolescents, stating that "depression is common among these populations and it is likely the sertraline will be used in children and adolescents, despite the absence of any relevant data." n41

n39 [HN11] **21 U.S.C. § 396** provides that "nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship." See, e.g., **Samarah v. Danek Med., Inc., 70 F. Supp. 2d 1196, 1209 n.7 (D. Kan. 1999)** (citing **Ortho Pharm. Corp. v. Cosprophar, Inc., 32 F.3d 690, 692 (2d Cir.1994)).**

n40 Geenens Deposition (Exhibit D) in Def.'s Failure To Warn App., Vol. 1 (Doc. # 224) at 58:24-59:3.

n41 Temple Letter (Exhibit V) in Def.'s Failure To Warn App., Vol. 2 (Doc. # 225).

[**25]
. Warnings

Throughout the time that Pfizer has marketed Zoloft in the United States, Zoloft prescriptions have included a package insert which lists "Precautions" and "Adverse Reactions." This package insert is reproduced in the Physician's Desk Reference.

Both the package insert and the PDR list precautions and clinical trial data on the risk of patients developing treatment-emergent suicidality, mania or hypomania, anxiety, nervousness, agitation, [*1106] hyperkinesia, insomnia, apathy, emotional lability and other potential adverse events. The package insert and PDR with regard to suicide have not changed, and the warnings which were in effect in July 1997 (at the time of Matthew's death) specifically noted: "Pediatric Use - Safety and effectiveness in children have not been established."

The package insert states in relevant part as follows:

PRECAUTIONS

General

Activation of Mania/Hypomania - During premarketing testing, hypomania or mania occurred in approximately 0.4% of ZOLOFT (sertraline hydrochloride) treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other [**26] marketed antidepressants. * * *

Suicide - The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for ZOLOFT should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. * * *

ADVERSE REACTIONS

Commonly Observed - The most commonly observed adverse events associated with the use of ZOLOFT (sertraline hydrochloride) and not seen at an equivalent incidence among placebo treated patients were: gastrointestinal complaints, including nausea, diarrhea/loose stools and dyspepsia; tremor; dizziness; insomnia; somnolence; increased sweating; dry mouth; and male sexual dysfunction (primarily ejaculatory delay).

Associated with Discontinuation of Treatment - Fifteen percent of 2710 subjects who received ZOLOFT in premarketing multiple dose clinical trials discontinued treatment due to an adverse event. The more common events (reported by at least 1% of subjects) associated with discontinuation included agitation, insomnia, male sexual dysfunction (primarily [**27] ejaculatory delay), somnolence, dizziness, headache, tremor, anorexia, diarrhea/loose stools, nausea, and fatigue.

Incidence in Controlled Clinical Trials - The table that follows enumerates adverse events that occurred at a frequency of 1% or more among ZOLOFT patients who participated in controlled trials comparing titrated ZOLOFT with placebo. Most patients received doses of 50 to 200 mg per day. The prescribed should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials

Adverse Experience (Percent of Patients Reporting)

ZOLOFT Placebo

(N=861) [**28] (N=853)

* * *

Centr. & Periph. Nerv. System Disorders

Headache 20.3 19.0

Dizziness 11.7 6.7
[*1107]

Tremor 10.7 2.7

Parethesia 2.0 1.8

Hypoesthesia 1.7 0.6

Twitching 1.4 0.1

Hypertonia 1.3 0.4

* * *

Psychiatric Disorders

Insomnia 16.4 8.8

Sexual Dysfunction-Male 15.5 2.2

Somnolence 13.4 5.9

Agitation 5.6 4.0

Nervousness 3.4 1.9

Anxiety 2.6 1.3

Yawning 1.9 0.2

Sexual Dysfunction-Female 1.7 0.2

Concentration Impaired 1.3 0.5

* * *

Other Events Observed During the Premarketing Evaluation of Zoloft (sertraline hydrochloride): During its premarketing assessment, multiple doses of ZOLOFT were administered to approximately 2700 subjects. The conditions and duration of exposure to ZOLOFT varied greatly, and included (in overlapping categories) clinical pharmacology studies, open and double-blind studies, uncontrolled and controlled studies,

inpatient and outpatient studies, fixed-dose and titration studies, and studies for indications other than depression. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, [**29] it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, a World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies reported, therefore, represent the proportion of the approximately 2700 individuals exposed to multiple doses of ZOLOFT who experienced an event of the type cited on at least one occasion while receiving ZOLOFT. All events are included except those already listed in the previous table and those reported in terms so general as to be uninformative. It is important to emphasize that although the events reported occurred during treatment with ZOLOFT, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo controlled trials appear in this [**30] listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are also described in the PRECAUTIONS section.
* * *

Central and Peripheral Nervous System Disorders - *Frequent*: confusion; *Infrequent*: ataxia, abnormal coordination, abnormal gait, hyperesthesia, hyperkinesia, hypokinesia. migraine, nystagmus, vertigo; *Rare*: local anesthesia, coma, convulsions, dyskinesia, dysphonia, hyporeflexia, hypotonia, ptosis. * * *

Psychiatric Disorders - *Infrequent*: abnormal dreams, aggressive reaction, amnesia, apathy, delusion, depersonalization, depression, aggravated depression, emotional lability, euphoria, hallucination, neurosis, paranoid reaction, suicide ideation and

attempt, teeth-grinding, abnormal thinking; *Rare*: hysteria, somnambulism, withdrawal syndrome.

According to the dictionary of the World Health Organization ("WHO"), "hyperkinesia" is the preferred term for akathisia.

At the time Pfizer issued the package insert warnings, they complied with FDA [*1108] regulatory standards, and the FDA mandated and approved them. n42 [HN12] Under [**31] **21 C.F.R. § 201.57(e)**, however, "the labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug," and a causal relationship need not have been proved. n43

n42 See Temple Letter (Exhibit V) in Def.'s Failure To Warn App., Vol. 2 (Doc. # 225); see also Leber Letter (Exhibit KK), Leber Letter (Exhibit LL), David Facsimile (Exhibit MM), Katz Letter (Exhibit NN), all in Def.'s Failure To Warn App., Vol. 4 (Doc. # 227).

n43 During the comment period on a new FDA labeling format, the FDA Commissioner stated that:

. . . these [HN13] labeling requirements do not prohibit a manufacturer, packer, relabeler, or distributor from warning health care professionals whenever possibly harmful adverse effects associated with the use of the drug are discovered. The addition to labeling and advertising of additional warnings, as well as contraindications, adverse reactions, and precautions regarding the drugs, or the issuance of letters directed to health care professionals (e.g. 'Dear Doctor' letters containing such information) is not prohibited by these regulations.

Labeling And Prescription Drug Advertising: Content And Format For Labeling for Human Consumption, 44 Fed. Reg. 37,434 (June 26, 1979) (Exhibit 51) in Plaintiffs' Pretrial Ex., Vol. II (Doc. # 369) at 37,447. Apparently the Commissioner (the record does not reveal who was commissioner at this time) was responding to these concerns after the FDA decided to adopt labeling standards.

[**32]

. Association Between Zoloft And Suicide n44

n44 In addition to the evidence discussed in this section, plaintiffs attempt to demonstrate an association between SSRI drugs and akathisia, and akathisia and suicide by citing The PDR Family Guide To Prescription Drugs (Exhibit 57), Prozac and Other Psychiatric Drugs, Everything You Need To Know by Dr. Lewis Opler (Pocket Books, 1996) (Exhibit 125), and Clinician's Handbook of Prescription Drugs by Sr. Seymour Ehrenpreis (2001) (Exhibit 139), all in Plaintiffs' Ex., Vol. IV (Doc. # 528). The Court has already sustained Pfizer's motion in limine as to The PDR Family Guide, and excluded it from evidence. Neither of the remaining books are listed on plaintiffs' exhibit list, relied upon by experts or shown to be admissible in evidence. The Court therefore disregards them as well.

When it approved the NDA for Zoloft for treatment of depression, the FDA issued a 60-page report, entitled "Summary Basis of Approval," which summarized the reasons [**33] and clinical data which supported its conclusion that Zoloft was safe and effective. n45 The FDA specifically addressed suicidality in section 5.2.2.4.1, stating:

n45 See Summary Basis of Approval (Exhibit EE) in Def.'s Failure To Warn App., Vol. 3 (Doc. # 226) at 38-39.

In the sertraline development program there were 9 suicide attempts in the sertraline group, 5 in the placebo group, and 1 in the active control group: all of these suicide attempts were in therapeutic depression studies. Two of the suicide attempts in the sertraline group resulted in completed suicides. The incidence rates by treatment group for suicide attempts, corrected for differential therapy duration, were 1.77 per 100 patient years (95% confidence limits 0.8-3.4) for the sertraline group, 2.39 (95% C.L. 0.7-5.5) in the placebo group, and 1.10 (95% C.L. 0.0-6.2) in the active control group. The incidence rates of suicide attempts were thus generally similar in the 3

treatment groups, with broadly overlapping 95% confidence [**34] limits. . . .

Review of the rates of events defined by baseline to endpoint shifts in HAM-D Item 3 scores [i.e., measurement of suicidal ideation] and baseline to endpoint changes in HAM-D Item 3 scores showed results favoring sertraline over placebo and supported the comparability of the sertraline [*1109] and active control groups with respect to suicidality in therapeutic depression trials.

According to Dr. Jonathan Cole, who gave deposition testimony in this case, such after-the-fact meta-analyses of clinical trial data are not designed to detect or measure treatment emergent suicidality. n46 Zoloft is a selective serotonin reuptake inhibitor ("SSRI") drug. n47 In the early 1990s, several medical and lay media reports suggested that Prozac - another SSRI drug (generally known as fluoxetine) - caused violent and suicidal activity. In particular, in February of 1990, psychiatrists Martin Teicher, M.D., Ph.D. and Jonathan Cole, M.D. (with nurse Carol Glod, R.N., M.S.C.S.) published an article which described six patients who reported suicidal ideation while undergoing treatment with Prozac and other medications. n48 The article theorized that their suicidal ideation was a paradoxical [**35] response to Prozac. After this article was published, the question whether SSRI antidepressants cause suicidal ideation or activity came to the forefront of public consciousness in the United States. This article, and the controversy which it created, engendered FDA regulatory action and captured the attention of the popular media. Initially this controversy was principally focused on Prozac - the only SSRI drug on the United States market at that time.

n46 See, e.g., Cole Declaration (Exhibit 3) in Plaintiffs' Pretrial Ex., Vol. I (Doc. # 368) at 4.

n47 See The Merck Manual of Diagnosis and Therapy (17th ed. 1999) at 1533-34.

n48 See Emergence Of Intense Suicidal Preoccupation During Fluoxetine Treatment, Am. J. Psychiatry 207-210 (Feb.

1990). Dr. Cole is an older physician; at one time (probably at least through 2000), he was considered a thought leader in psychopharmacology. According to Dr. Mann and Dr. Casey, Dr. Teicher is a pioneer in the field of psychopharmacology.

On October 10, 1990, the [**36] Citizens Commission on Human Rights, a group established by the Church of Scientology, petitioned the FDA to withdraw its approval of Prozac. On August 1, 1991, after reviewing the Scientology Petition and all available evidence, the FDA found that "the data and information available at this time do not indicate that Prozac causes suicidality or violent behavior." Peck Letter (Exhibit X) in Def.'s Failure To Warn Ex., Vol. 2 (Doc. # 225). Accordingly, it denied the petition. n49

n49 That same day, the American Psychiatric Association issued the following statement:

The Food and Drug Administration has chosen science over sensationalism by rejecting the petition of the Scientology-backed Citizens Commission on Human Rights to remove the antidepressant medicine Prozac from the market. The American Psychiatric Association applauds the FDA decision. . . . Like all prescription medicines, Prozac has some side effects. But it is depression, the illness, which kills by causing suicide in as many as one in six patients with major depression who are not being treated. . . . Psychiatrists and other physicians have known since medical school that treatment for depression, whether with anti-depressants or psychotherapy, may lead to an increase in energy before it eliminates the suicidal thoughts. Psychiatrists routinely alert patients and their families to this possibility, and urge them to contact their physician whenever they experience suicidal thoughts.

Statement by American Psychiatric Association on Aug. 1, 1991 (Exhibit QQ); see also News Release On Sept. 21, 1991 (Exhibit RR), both in Def.'s Failure To Warn App., Vol. 2 (Doc. # 227).

The most recent textbook by the American Psychiatric Association indicates that in approximately six per cent of the population, individuals who are treated with antidepressants will experience the appearance or worsening of suicidal behavior. Textbook Of Psychiatry (3rd ed. 1999) at 1398. It notes that Dr. Teicher and colleagues reported in 1990 that six depressed patients taking fluoxetine (Prozac) became intensely preoccupied with suicidal ideation and that fluoxetine-induced akathisia was implicated in several of those cases, on the basis of both the phenomenology of the symptom and a positive response to antiakathisia treatments. Other cases of increased suicidality were attributed to a well-known condition among severely depressed patients initiating treatment with antidepressants: relief from dysphoria may lag behind while energy levels begin to increase, with the result that the patients' motivation to complete suicide is greater than it was before treatment. The textbook concludes, however, that "whatever the explanation," studies of suicide rates among fluoxetine users have not indicated an increased risk of suicide attempts or completions, relative to users of other antidepressants; in fact, it notes that larger controlled studies have confirmed that suicide rates among depressed patients treated with fluoxetine (and all other antidepressants) are markedly reduced from those of depressed patients who do not receive antidepressants. See Excerpt from Textbook of Psychiatry (3d ed 1999) (Exhibit 27) in Plaintiffs' Pretrial Ex. Vol. I (Doc. # 368) at 1038-39, 1398-99.

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On May 23, 1991, Public Citizen, another group, petitioned the FDA to mandate a "black box" warning discussing the alleged causal connection between Prozac and suicide. n50 Four months later, on September 20, 1991, the FDA convened the 34th meeting of the PDAC to investigate the possibility that antidepressant drugs caused suicidal acts and thoughts, or other violent behavior. n51 As part of its meeting, the PDAC conducted a public hearing which lasted about four hours. After the hearing, the committee heard presentations from Eli Lilly which manufactures Prozac and FDA personnel. Upon reviewing the evidence, the PDAC unanimously concluded that there was

no credible evidence of a causal relationship between antidepressant drugs and the emergence and/or intensification of suicidality or other violent behavior. n52 [*1111] The PDAC voted (by a 6 to 3 vote) against recommending any change to package inserts for SSRI drugs. n53 In that regard, Dr. Leber, Director of the FDA Division of Neuropharmacological Drug Products (later FDA Commissioner), stated that a change in antidepressant labeling might have a "net effect [of] a reduction in the use of antidepressants in the treatment of depression, [**38] and that result might cause overall injury to the public health." n54

n50 See Peck Letter (Exhibit AA) in Def.'s Failure To Warn App., Vol. 2 (Doc. # 225).

n51 The FDA requested the committee's advice on the following:

(i) Is there credible evidence to support a conclusion that antidepressant drugs cause the emergence and/or intensification of suicidality and/or other violent behaviors?

(ii) If so, does the evidence indicate that a particular drug or drug class pose a greater risk than others?

(iii) If the whole class or a particular drug cause emergence and/or intensification of suicidality, what actions, if any, should the Agency take?

(iv) Even in the absence of sufficient evidence to establish causation, do the large volume of reports and/or the type of reports received justify some Agency action, e.g., a modification of labeling for some or all antidepressants?

Letter From M. Bernstein, M.D. To PDAC Members (Exhibit PP) in Def.'s Failure To Warn App., Vol. 4 (Doc. # 227).

Dr. Casey again chaired the committee, which included four members of the 33rd PDAC, which had reviewed Pfizer's NDA for Zoloft (Dr. Lieberman, Dr. Hammer, Dr. Tamminga and Dr. Escobar). New PDAC members included James Claghorn, M.D.

of Clinical Research Associates; David Dunner, M.D., professor in the Department of Psychiatry, University of Washington; Keh-Ming Lin, M.D., Director of Research on the Psychobiology of Ethnicity at the UCLA Medical Center; Regina Casper, M.D., professor of Psychiatry at the University of Chicago; and Nina Schooler, Ph.D., director of the Psychosis Research Program, Western Psychiatry Institute and Clinic, University of Pittsburgh. Consultants to the committee included Dr. Martin Teicher, whose case reports had given rise to the theory that Prozac caused suicidal behavior; Ida Hellander, M.D., one of the individuals who had signed the Public Citizen Petition; J. John Mann, M.D., professor of Psychiatry at the University of Pittsburgh (now at Columbia University); Stewart Montgomery, M.D., member of the Academic Department of Psychiatry of St. Mary's Hospital; Darrel A. Reiger, M.D., Director of the Division of Clinical Research, National Institute of Mental Health; and Michael Stanley, Ph.D. of Columbia University College of Physicians and Surgeons. Various FDA members (Michael Bernstein, M.P.H., Paul Leber, M.D., Robert Temple, M.D., Thomas Laughren, M.D. and Bruce Stadel, M.D.) also attended and participated. See Bernstein Letter To PDAC Members (Exhibit PP) in Def.'s Failure To Warn Ex., Vol 4 (Doc. # 227). [**39]

n52 See Transcript of Proceedings (Exhibit Z) in Def.'s Failure To Warn App., Vol. 2 (Doc. # 225) at 302.

n53 Id. at 331. The minority of members who voted to change the warnings opined that the change should be for *all* antidepressant drugs; none voted that the change should be limited to SSRI drugs. See PDAC Transcript (Exhibit Z) in Pfizer's Failure To Warn Ex., Vol. 2 (Doc. # 225) at 332:4-18.

n54 Id. at 129:16-19.

Upon reviewing the PDAC report, the FDA determined that while there was no reasonable evidence of a causal relationship between Prozac and suicide, more testing was appropriate. n55 At about the same time, in November of 1991, Dr. J. John Mann,

an eminent suicidologist and psychopharmacologist, published an article entitled Emergence Of Suicidal Ideation And Behavior During Antidepressant Pharmacotherapy. n56 In that article Dr. Mann proposed a three-way, randomized, double blind, placebo-controlled clinical trial to evaluate whether an antidepressant such as fluoxetine (Prozac) causes the emergence of suicidal ideation or intensifies [**40] existing suicidal ideation in certain patients. n57 He also proposed that future studies incorporate ratings for akathisia, anxiety, agitation, insomnia and other side effects to evaluate whether these side effects contributed to the emergence of suicidality in patients who received antidepressant therapy. n58 In conclusion, Dr. Mann stated:

n55 See June 3, 1992 Letter From C. Peck to I. Hellander And S. Wolfe On 6/3/92 (Exhibit AA) in Def.'s Failure To Warn App., Vol. 2 (Doc. # 225) at 17. The PDAC had also engaged in "a fair amount of discussion about the need for more research" on the question. Casey Deposition (Plaintiff's Ex. 17 at 15:17-16:3).

n56 Exhibit 23 in Plaintiffs' Ex., Vol. II (Doc. # 526) at 1031.

n57 That was the same type of test that Pfizer had conducted, analyzed and reported to the FDA more than a year earlier, and that Pfizer was continuing to conduct on an ongoing basis at the time Dr. Mann's article was published. See Summary Basis Of Approval (Exhibit 6) (data from RCT), Myers Report (Exhibit 12) (same), Ryder Report (Exhibit 37) (same), all in Pfizer's Pretrial Ex. Nos. 1-25 (Doc. # 228); and Appendix Of Exhibits (Nos. 26 To 51) To Defendant Pfizer Inc.'s Pretrial Motions ("Def.'s Pretrial Ex. Nos. 726-51"). [**41]

n58 Emergence Of Suicidal Ideation And Behavior During Antidepressant Pharmacotherapy (Exhibit 23) in Plaintiffs' Ex., Vol. II (Doc. # 526) at 1031; Mann Deposition (Exhibit 3) in Plaintiffs' Ex., Vol I (Doc. # 525) at 83-86. According to plaintiffs, Dr. Mann proposed that future studies incorporate ratings for akathisia and other side effects not to evaluate whether the side effects contributed to suicidality but

because this is the widely postulated "biologically plausible mechanism" which some believe will explain the paradoxical reaction of some patients becoming suicidal on SSRI drugs.

Plaintiffs insist that Pfizer has never performed a clinical trial or other test which uses the akathisia scale which Dr. Mann cites, or any other recognized measure of akathisia-like symptomatology to measure treatment-emergent agitation, restlessness, aggravation or akathisia among patients on Zoloft. Plaintiffs cite no record evidence for this proposition, and the Court disregards it. Furthermore, Dr. Mann testified that drug manufacturers have made a significant effort to see if a relationship exists between "the use of agents like SSRIs and suicidal behavior using a variety of strategies." Mann Deposition (Exhibit 3) in Plaintiffs' Ex., Vol I (Doc. # 525) at 147-48.

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Clinicians should be aware that emergence or intensification of suicidal ideation and behavior in patients receiving antidepressant treatment has been reported. . . . Whether certain antidepressants precipitate or aggravate suicidal ideation in a small, vulnerable subpopulation of psychiatric patients who require antidepressants is uncertain. In practice, whatever the antidepressant medication, the clinician should always monitor the patient to assess the severity of the depression and suicidal ideation, aggressive ideation or behavior, agitation and akathisia. Paradoxical suicidal ideation or behavior may be more frequent in nonresponders, patients with unrecognized akathisia, and patients with histories of attempted suicide. Therefore, the clinician should continue informing patients with depression who are being treated with antidepressant medications that depressive symptoms and/or a worsening or emergence of suicidal ideation may occasionally occur during treatment. The patient should be instructed to immediately inform the clinician should symptoms occur. The clinician can then judge whether the cause is the illness, the environment, or the treatment. n59

n59 Plaintiffs claim that in his article, Dr. Mann recommended "warnings or advice to patients and physicians

concerning the potential for SSRI-induced suicide." The Court, however, does not find that plaintiffs' citations actually stand for this point. In his article, Dr. Mann concluded that "the clinician should continue informing patients with depression who are being treated with antidepressant medications that depressive symptoms and/or a worsening or emergence of suicidal ideation may occasionally occur during treatment." Emergence Of Suicidal Ideation And Behavior During Antidepressant Pharmacotherpy [sic] (Exhibit 23) in Plaintiffs' Ex., Vol. II (Doc. # 526) at 1032. Dr. Mann also stated that suicidal ideation and behavior have not been associated with any particular antidepressant and it is uncertain whether certain antidepressants precipitate or aggravate suicidal ideation. Id.

[**43]

After he wrote that article, Dr. Mann obtained sertraline placebo and active-control suicidal ideation and attempt data from randomized, double blind, placebo-controlled clinical trials by Pfizer - along with similar data for other SSRI and non-SSRI drugs. On March 2, 1992, four months after the earlier article, Dr. Mann co-authored a second article which was accepted as a consensus statement by the American College of Neuropsychopharmacology ("ACNP"). In that article, Dr. Mann reviewed in detail the Pfizer data, with the similar data for other SSRI and non-SSRI drugs. Having done so, Dr. Mann and his co-authors reached the following conclusions in the ACNP consensus statement:

In conclusion, case reports suggest that a small minority of patients may experience emergent suicidal thoughts or evince such behavior during the pharmacological treatment of depression. These reports do not distinguish between the relative potential contribution of the disease process, external stressors, or the medication. Of significance, there is evidence that such emergent suicidality is not specific to any one type of antidepressant and may therefore be largely a manifestation of the natural [**44] course of the illness. . . . There is no evidence that antidepressants such as the selective serotonin reuptake inhibitors, for example, fluoxetine [Prozac], trigger emergent suicidal ideation over and above rates that may be

associated with depression and other antidepressants. What is clear is that most patients receive substantial benefit from treatment with this drug and related antidepressants.
[*1113]

It is good clinical practice to monitor patients receiving treatment with antidepressants with regard to general clinical progress, and in particular, suicidal ideation and impulses. It is well known that depressed patients who are responding to treatment may occasionally have brief relapses lasting one or two days in which their symptoms may recur. Side effects such as akathisia may be associated with a worsening psychiatric state. Patients should be warned that suicidal ideation may occasionally worsen in the course of treatment, as may overall depression, and that such an event would be reason for immediately contacting their doctor. Applying this standard clinical to all patients would constitute a reasonable safeguard in the event that there are, indeed, a small minority of [**45] vulnerable patients who are at risk for emergent suicidal ideation. It should be recognized that such emergent suicidal ideation may be the consequence of the patient's illness, adverse changes in the life situation, or, perhaps, in a few cases, because of an adverse effect of the antidepressant. n60

n60 Suicidal Behavior And Psychotropic Medication (accepted as a Consensus Statement by the ACNP Council, March 2, 1992) (Exhibit SS) in Def.'s Failure To Warn App., Vol. 4 (Doc. # 227) at 180, 182.

Plaintiffs claim that according to Dr. Mann, the consensus of the ACNP called for testing and warnings about the possible dangers of antidepressant-induced suicide. The record evidence, however, does not support such a statement. Indeed, when asked if the consensus of the ACNP was that more testing and research needed to be done, Dr. Mann stated "that wasn't in the formal conclusion section," "I don't think one can make such a specific reading of this language," and "the spirit of the communication is that gathering information using one or more of these strategies is a good idea." Mann Deposition (Exhibit 3) in Plaintiffs' Ex., Vol. I (Doc. # 525) at 135-38. Because plaintiffs

cite no record evidence for their proposition, the Court must disregard it.

[**46]

At his deposition, Dr. Mann confirmed his personal belief that neuroleptic-induced akathisia (the classic form of akathisia which is associated with antipsychotic medication) is a risk factor for suicidal behavior. Questioned whether SSRI drugs cause akathisia in some patients, he responded:

SSRI drugs in some patients cause some kind of feelings of agitation, which may include some motor manifestations. It's not clear that it's exactly the same syndrome that you see in people who take antipsychotic medications, which is where akathisia was classically described. There may be an overlap, but it doesn't appear to be exactly the same type of thing. n61

n61 Mann Deposition (Exhibit 3) in Plaintiffs' Ex., Vol. I (Doc. # 525) at 85:22-86:22, 88:9-19, 166:16-167:4, 169:10-20, 170:6-171:12.

Dr. Mann also testified that the warning regarding suicide risk, along with the other adverse reaction information provided in the Zoloft package insert, was adequate to inform physicians' clinical judgments [**47] in prescribing Zoloft and that Pfizer's warnings were entirely consistent with the recommendation in the ACNP paper. n62

n62 Mann Deposition (Exhibit 3) in Plaintiffs' Ex., Vol. I (Doc. # 525) at 174:18-175:19.

Meanwhile, in March of 1991, Eli Lilly had drafted a study protocol on this issue and submitted it to the FDA. In the proposed study, Eli Lilly rejected the classic randomized controlled trial design in favor of a challenge-rechallenge study design to test whether antidepressants trigger emergent suicidal ideation or acts. n63

n63 In general, with appropriate consent forms and safeguards, "challenge-dechallenge-rechallenge" is a scientifically accepted manner of establishing causation with regard to certain side effects of drugs. Plaintiffs cite no evidence, however, that the FDA, or any ethics committee or institutional review board, approved the Eli Lilly study protocol. It is clear that such a study design poses major ethical issues, for it requires "rechallenging" patients with medication to see if they experience suicidal ideation or commit suicidal acts. See Testimony Of Dr. John Davis (Exhibit 1) in Declaration OF Katherine E. Sweeney ("Sweeney Declaration") (Doc. # 555) filed December 5, 2001 at 33:8-34:1 ("it would be hard to justify to an ethical review board putting patients on a drug with the purpose of measuring how many kill themselves"); Mann Deposition (Exhibit 3) in Plaintiffs' Ex., Vol. I (Doc. # 525) at 156:6-24 (prospective studies into causal effect of suicide would not be approved by an ethical review board).

[*1114]
[**48]

On June 3, 1992, when no PDAC member agreed that "there is evidence to indicate that a particular drug or drug class poses a greater risk for the emergence and/or intensification of suicidal thoughts and acts and/or other violent behaviors," the FDA denied the Public Citizen Petition. It accordingly concluded that a change in labeling was not warranted at that time. n64

n64 See PDAC Transcript (Exhibit Z) in Def.'s Failure To Warn App., Vol. 2 (Doc. # 225) at 302.

In 1998, the Textbook of Psychopharmacology summarized the state of the matter as follows: Several reviews have examined the data relevant to the question of whether antidepressant pharmacotherapy is associated with the emergence of suicidal ideation and behavior. These studies indicate that although suicidal ideation may emerge rarely during antidepressant treatment of depressed patients, these responses occur with essentially all types of antidepressant drugs, and a causal

relationship to antidepressant drugs has not been established. [**49] n65

n65 A. Schatzberg & C. Nemeroff, Textbook of Psychopharmacology (2d Ed. 1998) at 717.

In 2000, plaintiffs' expert, Dr. Morton Silverman, published a book which stated:

Shortly after the market introduction of fluoxetine, a small number of case reports (e.g., Teicher, Glod, & Cole, 1990) noted the emergence of suicidal ideation in patients taking fluoxetine. A great deal of publicity in the media surrounded such reports, which hypothesized that fluoxetine may trigger emergent suicidal and homicidal ideation in a small proportion of patients taking this medication. Further study has clarified that there is no 'increased risk of suicidal acts or emergence of substantial suicidal thoughts among depressed patients' associated with the treatment of fluoxetine (Beasley et al., 1991). The American College of Neuropsychopharmacology Task Force review of suicidal behavior and psychotropic medication concluded that "new generation low-toxicity antidepressants, including SSRIs, may carry a lower risk for [**50] suicide than older TCAs [tricyclic antidepressants]. There is no evidence that antidepressants such as the SSRIs, for example fluoxetine, trigger emergent suicidal ideation over and above rates that may be associated with depression and other antidepressants. What is clear is that most patients receive substantial benefit from treatment with this drug and related antidepressants. (Mann, Goodwin, O'Brien, & Robinson, 1993, p. 182) Other new agents have proven to be valuable additions to the antidepressant armamentarium. Sertraline (Zoloft), paroxetine (Paxil), bupropion (Wellbutrin), venlafaxine (Effexor), nefazadone (Serzone), citalopram (Celexa), and mirtazapine (Remeron) appear to be equally effective in the treatment of depression and usually are well tolerated with relatively few side effects. n66

n66 M. Goldblatt & M. Silverman, Psychopharmacological Treatment of Suicidal Patients (Chapter

6), in Review of Suicidology (Guilford 1999) (R. Maris, S. Canetto, J. McIntosh, M. Silverman eds.) at 143-44.

[*1115]
[**51]

In clinical testing of Zoloft, Pfizer has monitored reports of adverse events to determine whether there are epidemiological signals that Zoloft may cause suicide. Also, shortly after it launched Zoloft, Pfizer formed an internal "Issues Preparedness Committee." n67 The committee, which met approximately every two weeks in early 1992, examined allegations regarding SSRI drugs and suicide and violence in 1992, and specifically monitored adverse event reports regarding Zoloft and suicide. On a month by month basis, they tracked reports which associated suicidal ideation and attempts with Zoloft therapy, and compared the number of such reports with the rising numbers of Zoloft prescriptions and patients being treated with Zoloft, to assess whether reports of suicidality increased in proportion to the increasing use of Zoloft. As Zoloft prescriptions skyrocketed, reports of suicidal ideation and attempts remained consistently few in number; they did not rise at all, much less in proportion to increasing Zoloft usage. n68

n67 Members of the committee included Dr. Gretchen Dieck, a Yale-trained epidemiologist who heads Pfizer's Worldwide Safety department, and physicians and scientists who work in her department. [**52]

n68 Dr. Dieck testified that Pfizer's Worldwide Safety Department uses a "reasonable possibility" in determining whether to warn about a potential adverse outcome caused by a medication. Deposition Of Gretchen Dieck (Exhibit 13) in Plaintiffs' Ex., Vol. I (Doc. # 525) at 94:7-95:15. Any change to the label, however, must be approved by the FDA through a consensus process with the drug manufacturer. See id. at 95:23-97:8.

In May 1992, Pfizer again analyzed its clinical database, which by then included more than 3300 patients. Its analysis found a lower incidence of suicide attempts in Zoloft-treated patients

(.28%) than in placebo patients (.32%). It also found consistent improvement in measures of suicidal ideation in Zoloft-treated patients. n69 In June 1992, the results of this analysis were published and presented at the Collegium Internationale Neuro-Psychopharmacologicum, an international medical conference. n70 In addition, on June 19, 1992, Pfizer assembled a group of leading outside experts to independently review the Zoloft safety databases, examine whether further analysis [**53] of existing data might be useful, and discuss options for generating new data. n71

n69 See Ryder Report (Exhibit UU) in Def.'s Failure To Warn App., Vol. 4 (Doc. # 227) at 1-2, 12.

n70 To the best of Pfizer's knowledge, the data and methodology in this analysis have not been challenged in any published medical literature in the intervening eight years.

n71 Members of the expert panel included Dr. Daniel Casey, who had chaired the FDA's 33rd and 34th PDAC meetings; Dr. Jan Fawcett, who had represented Eli Lilly at the PDAC meeting on September 20, 1991; Dr. Richard Shader from Tufts University; Dr. Alec Walker, an epidemiologist from Harvard University; and Dr. Myrna Weissman. Casey Deposition (Exhibit WW) in Def.'s Failure To Warn App., Vol. 4 (Doc. # 227) at 29:22-24.

In early 1993 an eight-year-old boy was taking Zoloft in a clinical trial which began on January 21, 1992. Before he enrolled in the trial and began to take Zoloft, he had been clinically depressed, sad and irritable [**54] for a period of three years, beginning after his parents' divorce. He had insomnia at least three times a week and was agitated, fidgety and restless. Just before he began the study, he told his mother, "I would be better off dead." For the prior two and one-half years, he had been treated with psychotherapy without medication. His mother had a history of depression, and her 19-year-old brother had committed suicide. The child initially responded [*1116] well to Zoloft. In late February of 1993, however, his behavior and mood remarkably changed - his

mother said that he had increased energy, was very irritable and was "looking for a fight." On February 27, his mother reported that her son had recently put a necktie very tightly around his neck, leaving marks on his neck, and cut his feet with razor blades. The boy was admitted to the hospital and a clinical investigator for Pfizer spoke to the admitting physician by telephone. The investigator made a written note that "over the phone, it seemed to me as if the patient had become manic on 200 mg of Zoloft." Pfizer reported this information to the FDA. n72

n72 Patient's Notes (Exhibit 16) in Plaintiffs' Ex., Vol. I (Doc. # 525) at 017085.

[**55]

As of May 28, 1996, Pfizer had applied to the FDA for permission to market Zoloft for treatment of pediatric obsessive compulsive disorder ("OCD"). In that regard, on that date, Pfizer submitted reports which specifically reviewed the incidence of suicide ideation, gestures and attempts among Zoloft patients in adult and pediatric OCD development programs. Pfizer reported that in the adult program, eight of 1,581 patients who were treated with sertraline (0.51%) experienced serious suicide-related events (gestures, attempts or ideation), while three of 426 patients who received placebos (0.7 %) and three of 308 patients who received an active control drug (0.97%) experienced such events. In the pediatric program for patients with OCD but not depression, patients who were in the sertraline group experienced no serious suicide-related events; the placebo group experienced one event. In the pediatric OCD program overall (portions of which did not include placebo control, and which included pediatric patients with depression or both OCD and depression), six out of 220 sertraline patients, all of whom had multiple risk factors for suicidal behavior, reported suicide attempts or ideation. [**56] The frequency rate for this group (2.7%) was identical to the rate reported for suicide attempts requiring medical care in a nationwide sample of adolescents unselected for any psychiatric or behavioral problem. n73

n73 See Letter From Dr. Martha Brumfield, Pfizer Inc. To Paul Leber (Enclosure 1: Suicide-Related Behaviors in Adults in the Sertraline Obsessive-Compulsive Disorder Clinical Development Program, Enclosure 2: Suicide-Related Behavior in Children and Adolescents in the Sertraline OCD Clinical Development Program) (Exhibit XX) in Def.'s Failure To Warn App., Vol. 4 (Doc. # 227).

On October 10, 1997, the FDA approved Zoloft as safe and effective for treatment of pediatric OCD. n74 Pfizer reported that the rate of suicidal events on Zoloft vs. placebo for children was 2.7:1 - the same as the rate of suicidal events in children who were not being treated for psychiatric or behavioral problems nationwide. n75

n74 See Fax From Paul David On October 10, 1997 (Exhibit MM) in Def.'s Failure To Warn App., Vol. 4 (Doc. # 227) [**57]

n75 See Suicide-Related Behaviors In Children And Adolescents In The Sertraline OCD Clinical Development Program (attached to Brumfield Letter) (Exhibit 40) in Pfizer's Pretrial Ex. Nos. 1-50 (Doc. # 229) at 18. The Court is confused by plaintiffs' argument that Pfizer ignored the "placebo control" for its pediatric group in calculating this number. Plaintiffs assert that there was only one suicidal attempt on placebo, and that the suicide attempt rate on sertraline is actually quite higher than that of placebo. In reviewing this study, however, the Court notes that Protocol 498 (which had the placebo suicidal attempt that plaintiffs refer to, i.e. one adverse reaction out of 95 placebo treated subjects) had no adverse reactions among the 92 sertraline-treated subjects. See id. at 11. Plaintiffs apparently reach their conclusion by adding the numbers from all studies in which only sertraline and not placebo is used. Plaintiffs do not explain why this calculation is valid and it is unreasonable to add suicide attempts from other sertraline studies without adding suicide attempts from other placebo studies (or extrapolating from the placebo study at hand what the number might be). Pfizer's study did admit, however, that as to one patient,

sertraline probably caused the adverse event when few other risk factors were present aside from a family history of depression and suicide and early onset of depression in the patient. See Adverse Experience Report (Exhibit 40) in Def.'s Pretrial Ex. Nos. 26-51 Vol. II (Doc. # 526) at 17-18.

[*1117]
[**58]

In 1998, Pfizer's Dr. Roger Lane wrote and published an article entitled SSRI-Induced Extrapyramidal Reactions and Akathisia: Implications For Treatment, which was pre-reviewed and approved by Pfizer's Publications Committee. n76 The article concluded that although no definite association had been established between SSRI drugs and extrapyramidal side effects (EPS), SSRI drugs "may occasionally induce" such side effects and/or akathisia. Table 3 of the article listed 28 references to akathisia, seven of which purportedly involve a report of akathisia in a patient taking Zoloft. n77 In compiling those references, Dr. Lane employed "the loosest definition of akathisia" in order to include "all case reports. . . . even case reports where they didn't actually say 'akathisia,' but that may have been construed as constituting what some people define as akathisia."

n76 Exhibit 22 in Plaintiffs' Ex., Vol. II (Doc. # 526). Although the article was published after Matthew's death, it relied on anecdotal case reports which preceded July, 1991.

n77 Id. at 197-98.

[**59]

In July of 1999, at the request of the Irish Medicines Board ("IMB"), Pfizer conducted an analysis of its computer database of adverse events related to "suicide events," which the analysis defined as actual suicides and suicidal ideation, gestures and attempts. On at least 54 occasions, the clinical investigator and/or internal Pfizer reviewer determined that a suicide was related to Zoloft, or that the cause of the suicide was unknown. n78 After reviewing all 54 cases, Pfizer's report for the IMB concluded that the events did not demonstrate a causal

relationship between Zoloft and suicide. The IMB agreed, and found that the evidence did not warrant additional or different warnings or other regulatory action. n79

n78 See Sertraline And Suicide-Related Events (Exhibit 115) in Plaintiffs' Ex., Vol. IV (Doc. # 527) at 4. In its Response To Plaintiffs' Supplemental Memorandum Explaining Significance Of Pfizer's IMB Report (Docs. # 476 and 477) filed January 22, 2001, Pfizer explained that the study protocol required investigators to attribute an adverse reaction to the study drug if they discerned a mere possibility of a causal relationship, or when they considered the cause of the event to be unknown or certain. Pfizer incorporates that response in its opposition to plaintiffs' motion for partial summary judgment. [**60]

n79 According to Pfizer's report for the IMB report, there were 252 suicidal events during the Zoloft clinical trials, and 21% of them were deemed related to Zoloft by a clinical investigator, internal Pfizer reviewer, or both. Pfizer investigated these events. As to one patient who experienced a panic reaction and tried to commit suicide by intentional overdose, the Pfizer Safety Committee concluded that it was "reasonably possible" that these events are associated with study drugs." See Sertraline And Suicide-Related Events (Exhibit 115) in Plaintiffs' Ex., Vol. IV (Doc. # 527) at 11.

Plaintiffs cite the most recent version of the American Psychiatric Association's Diagnostic and Statistical Manual [DSM-IV-TR], which states that

Serotonin-specific reuptake inhibitor antidepressant medications may produce akathisia that appears to be identical in phenomenology and treatment response to Neuroleptic-Induced Acute Akathisia. . . . The subjective distress resulting from akathisia is significant . . . [and] may be associated with dysphoria, irritability, aggression, or suicide [**61] attempts. n80

n80 Exhibit 4 in Plaintiff's Ex., Vol. I (Doc. # 525) at 333.99.

[*1118]

This language appears only in Appendix B, however, which lists the provisions that the DSM-IV task Force did *not* adopt. n81

n81 Appendix B contains a number of proposals for new categories and axis that were suggested for possible inclusion in DSM-IV. According to the manual, the DSM-IV Task Force and Work Group subjected each proposal to a careful empirical review and invited wide commentary from the field, but determined that there was insufficient information to warrant inclusion of the listed proposals as official categories or axis in DSM-IV.

Plaintiffs' expert, Dr. David Healy, has attested that some researchers have written that "there are grounds to suspect that some individuals may become suicidal on antidepressants." n82 Furthermore, [**62] he has opined that SSRI-induced akathisia sometimes leads to suicide and, in Matthew's case, that it triggered his suicide. n83

n82 Healy Declaration (Exhibit 2) in Plaintiffs' Pretrial Ex., Vol. I (Doc. # 368) at P 26.

n83 Plaintiffs' response to Pfizer's statement of facts in its motion for summary judgment on their failure to warn claim includes responses to facts numbered 77 to 93. When Pfizer re-filed this brief, however, it apparently revised its factual assertions to end at 76. The Court therefore disregards plaintiffs' extraneous arguments as irrelevant to Pfizer's motion.

. Proceedings In This Case

On January 24, 2000, plaintiffs filed their amended complaint in this matter. Count I alleges that Pfizer is strictly liable for marketing defects and misrepresentations concerning Zoloft. Count II alleges that Pfizer is liable under common law

negligence theories for failure to test and warn about the dangers of Zoloft-induced suicide. [HN14] In Kansas, product liability claims are governed by [**63] the Kansas Products Liability Act ("KPLA"), K.S.A. § 60-3301 et seq. The purpose of the KPLA is "to consolidate all product liability actions, regardless of theory, into one theory of legal liability." **Samarah, 70 F. Supp. 2d at 1202; Patton v. Hutchinson Wil-Rich Mfg. Co., 253 Kan. 741, 756, 861 P.2d 1299, 1311 (1993).** Under K.S.A. § 60-3302(c), "all legal theories of recovery, e.g., negligence, strict liability, and failure to warn, are to be merged into one legal theory called a 'product liability claim.'" **Samarah, 70 F. Supp. 2d at 1202; Savina v. Sterling Drug, Inc., 247 Kan. 105, 127, 795 P.2d 915, 931 (1990)** (KPLA provisions apply to actions based on strict liability as well as negligence, breach of express or implied warranty, and breach of or failure to discharge duty to warn or instruct).

In the pretrial order, plaintiffs allege that Pfizer should have warned of the risks of "akathisia," "emotional blunting or disinhibition," "mania, hypomania, psychosis" and "serotonin syndrome," and the fact that these physical reactions to Zoloft "can cause some people to react in violent or suicidal ways." n84 Dr. [**64] Donald Marks, plaintiffs' warnings expert, opines that Pfizer acted in an unreasonable manner by not providing "prominent and adequate warnings about the risks of akathisia and suicide and . . . cautioning physicians that [Zoloft] had not been adequately tested or approved for use in children and adolescents." n85 According to Dr. Marks, Pfizer should have warned that "adverse events, including suicide, suicide ideation, akathisia and emotional blunting, . . . have been [*1119] found to occur in [a] small number of patients," that these symptoms could be due to Zoloft rather than the underlying depression and that they should be treated as such. n86 Dr. Marks admitted, however, that Dr. Healy's report did not support a conclusion that Pfizer should have warned about or tested for emotional blunting, but he believed Pfizer should have tested for a causal relationship between Zoloft and suicide and suicidal ideation. n87

n84 Pretrial Order (Doc. # 171) filed March 6, 2000 at 3-4.

n85 Expert Report Of Dr. Donald Marks, M.D., Ph.D. (Exhibit R) in Def.'s Failure To Warn App., Vol. 2 (Doc. # 225) at 1-2. Dr. Marks testified that the FDA imposes a duty to warn when there is a "reasonable probability" of a causal connection which means more likely than not caused by the drug. See id. at 259:20-260:3. Dr. Marks also admitted that it was his opinion that, if the FDA had concluded that there was not a reasonable probability of causal relationship between Zoloft and suicide, there was no duty to warn or to test. See id. at 260:20-261:14. [**65]

n86 Deposition of Donald Marks (Exhibit S) in Def.'s Failure To Warn App., Vol. 2 (Doc. # 225) at 222:22-224:3.

n87 Id. at 228:12-20; 224-29. Dr. Marks has not drafted specific warnings that he believes Pfizer should have used. Id. at 205:13-18. Nor has he expressed any opinions as to where in the Zoloft package insert a hypothetical warning should go. Id. at 205:19-25.

Analysis

I. Defendant Pfizer Inc.'s Motion For Partial Summary Judgement On Plaintiffs' Claim Of Marketing Defect and Misrepresentations (Count I) (Doc. # 505)

Plaintiffs assert that Pfizer "has gone to great lengths to reassure doctors that the violence and suicide problems which they have heard about, mainly with its chief SSRI competitor Prozac, would not occur with Zoloft, and to assuage patient's concerns over the initial adverse effects which are frequently the harbingers of tragedy" and that this constitutes a misrepresentation of material facts. Pretrial Order (Doc. # 171) at 4. Plaintiffs do not more specifically identify a particular theory of fraudulent misrepresentation, nor [**66] do they more specifically explain any alleged so-called "marketing defect" claim. The Court therefore construes Count I as strictly a fraud count and finds that, so construed, the allegations do not satisfy the pleading requirements of Rule 9(b), Fed. R. Civ. P. Moreover, plaintiffs have cited absolutely no evidence of "great

lengths" to which Pfizer has resorted to reassure doctors in general - or Dr. Geenens in particular - that "violence and suicide problems . . . would not occur with Zoloft." Count I therefore suffers a fatal failure of proof.

In seeking summary judgment, Pfizer first argues that plaintiffs cannot show detrimental reliance on any misrepresentation. n88 [HN15] To sustain an action for fraud or misrepresentation in Kansas, plaintiffs must establish among other things that they reasonably relied and acted on the allegedly false representations to their detriment. See PIK-Civil 3d 127.40 (reasonable reliance required for fraud), 127.43 (reliance required for negligent misrepresentation); **Canterbury Ct., Inc., v. Rosenberg, 224 Kan. 493, 503, 582 P.2d 261, 269-70 (1978)** (party to whom misrepresentation is made must rely and act upon it to his detriment); [**67] **Todd v. Wichita Fed. Savings & Loan Assoc., 184 Kan. 492, 494, 337 P.2d 648, 650 (1959)** (to secure redress for false representations, plaintiff must show that they were relied upon to his detriment); see also **Samarah, 70 F. Supp. 2d at 1209 (1999)** (no evidence that treating physician relied on representations regarding suitability of medical device for particular use, plaintiff could not establish element of reliance necessary for recovery on claim for fraud). Pfizer notes that the pretrial order contains no allegation that Dr. Geenens relied on fraudulent materials and, indeed, Dr. Geenens has submitted sworn testimony that he did not rely on any marketing materials from Pfizer.

n88 Although Pfizer discusses the reliance prong of misrepresentation, it does not concede that it made any misrepresentations to Dr. Geenens, plaintiffs or Matthew Miller.

[*1120]

Pfizer next claims that even if plaintiffs had evidence of reliance, the "learned intermediary" doctrine means that Pfizer [**68] only had a duty to provide information to Dr. Geenens, not plaintiffs. Pfizer asserts that it is entitled to summary judgment because plaintiffs have not alleged or proved that Dr. Geenens, their learned intermediary, relied on any misrepresentations by Pfizer.

Plaintiffs respond that (1) they do not need to show reliance because Kansas has adopted a strict liability approach to products liability misrepresentation actions; (2) Kansas could also adopt Section 9 of the "Restatement (Third) of Torts: Products Liability" and hold manufacturers liable for innocent misrepresentations without proof of reliance; (3) the Kansas Supreme Court is likely to find that K.S.A. § 60-3305 has overruled the learned intermediary doctrine; n89 and (4) if plaintiffs are required to prove reliance, they can do so.

In support of their claim that they do not need to prove reliance because Kansas has adopted a strict liability approach to products liability misrepresentation actions, plaintiffs cite **Hurlbut v. Conoco, 253 Kan. 515, 521, 856 P.2d 1313, 1320 (1993).** Specifically, plaintiffs argue that in 1993, the Kansas Supreme Court mentioned strict products liability, particularly [**69] with regard to a misrepresentation claim, as a viable form of recovery. In Hurlbut, the Kansas Supreme Court noted that because plaintiff had alleged strict liability, he claimed that he did not need to determine which of two possible causes (only one of which involved defendant's product) had produced the explosion that precipitated his lawsuit. See id. The trial court overruled defendant's motion for summary judgment even though plaintiff had not set forth facts or calculations on which his experts relied to prove liability. See id. The case proceeded to trial and after a plaintiff's verdict, defendant appealed the denial of its summary judgment motion. See **id. at 518-19, 856 P.2d at 1320.** On appeal, however, causation rather than reliance was at issue. n90 Therefore Hurlbut does not stand for the proposition that plaintiffs do not need to show reliance in product liability misrepresentation actions.

n89 Plaintiffs' Misrepresentation Response (Doc. # 516) at 8 n.1.

n90 Hurlbut is somewhat confusing because it appears that the Kansas Supreme Court relied on expert testimony at trial in determining that defendant's pretrial summary judgment motion was properly denied. In that regard, the Kansas Supreme Court treated defendant's summary judgment motion more like a motion for judgment as a matter of law. It dealt separately,

however, with defendant's motion for judgment as a matter of law. The issue is particularly confusing in light of the fact that a denial of summary judgment is typically not subject to appellate review. See **Matter of Ziebell's Estate, 2 Kan. App. 2d 99, 101, 575 P.2d 574, 576 (1979).**

[**70]

In arguing that proof of reliance is not necessary, plaintiffs also rely on Section 9 of the "Restatement (Third) of Torts: Products Liability," which states that manufacturers could be liable for even innocent misrepresentations of material fact. Pfizer points out that Kansas has not adopted the Third Restatement (or otherwise imposed strict liability for innocent misrepresentations) and that even if it had done so, the Third Restatement requires proof that plaintiffs' injury was "caused by the misrepresentation." n91 Citing **Delaney v. Deere and Company,** [*1121] **268 Kan. 769, 793, 999 P.2d 930, 946,** plaintiffs argue that if Kansas has not imposed strict liability for innocent misrepresentations, it is only because Kansas favors an even more pro-consumer strict liability stance. In Delaney v. Deere, the Kansas Supreme Court declined to adopt Comment l of Section 9 of the Third Restatement because Section 9 would have required Kansas to adopt the reasonable alternative design standard - and an exclusive risk/utility analysis of that reasonable alternative design - to determine whether a subject product is defective. See id. The Kansas Supreme Court decided that [HN16] in Kansas, "the ultimate [**71] determination remains whether the product is defective and dangerous beyond a reasonable consumer's expectations." Id.

n91 Memorandum In Support Of Motion For Partial Summary Judgment On Plaintiff's Claim Of Marketing Defect And Misrepresentation ("Pfizer's Misrepresentation Memorandum") (Doc. # 506) filed September 12, 2001 at 9 (citing Restatement Of Torts 3d § 9, Comment c).

Pfizer also asserts that the Kansas Supreme Court has explicitly rejected the Third Restatement, see **Delaney v. Deere & Co., 268 Kan. at 793, 999 P.2d at 946,** and that for this Court to apply it would violate the fundamental principles of **Erie R.**

Co. v. Tompkins, 304 U.S. 64, 82 L. Ed. 1188, 58 S. Ct. 817 (1938). Pfizer also contends that the trend in Kansas law, as evidenced by the Kansas Product Liability Act, is to limit the rights of recovery in products liability suits. See Pfizer's Misrepresentation Reply (Doc. # 519) at 10 n.8 (citing **Patton v. Hutchinson Wil-Rich Mfg. Co., 253 Kan. 741, 861 P.2d 1299 at 1309 (Kan. 1993)).**

[**72]

In this case, however, plaintiffs' argument is unavailing because the Third Restatement requires proof that plaintiffs' injury was "caused by the misrepresentation," and the Kansas Supreme Court has noted that [HN17] "the reliance element of misrepresentation serves the function of causation in fact: that the misrepresentation causes someone to act or refrain from acting." **Tetuan v. A.H. Robins Co., 241 Kan. 441, 468, 738 P.2d 1210, 1230 (1987)** (quoting Restatement (Second) of Torts § 546, Comment b). For plaintiffs to recover for misrepresentation under Kansas law, they must show reliance.

Regarding Pfizer's learned intermediary argument, that doctrine has been summarized as follows:

[HN18] Under the learned intermediary doctrine, a prescription drug manufacturer's duty to warn "is satisfied when the prescribing doctor is informed of a drug's inherent risks." **Nichols v. Central Merch., Inc., 16 Kan. App. 2d 65, 67, 817 P.2d 1131, 1133 (1991).** According to the Kansas Supreme Court, the "rule is based upon the theory that the physician acts as a learned intermediary between the drug manufacturer and the patient." **Humes v. Clinton, 246 Kan. 590, 600, 792 P.2d 1032, 1039 (1990).** [**73] Because "prescription drugs are available only to a physician, it is the physician's duty to inform himself or herself of the characteristics of the drugs prescribed and to exercise his or her judgment of which drug to administer in light of the drug's propensities and the patient's susceptibilities." Id. The learned intermediary doctrine allows the manufacturer to "assume a patient places reliance on the physician's judgment and relieves the manufacturer of a duty to assist the physician in communicating with patients." **Id. at 601,**

792 P.2d at 1039. In analyzing whether a warning is sufficiently adequate to inform the treating physician, a court must determine "whether the warning is 'reasonable under the circumstances.'" **Id. at 606, 792 P.2d at 1043.**

Samarah, 70 F. Supp. 2d at 1204.

In support of their claim that the Kansas Supreme Court is likely to find that K.S.A. § 60-3305 has overruled the learned intermediary doctrine, plaintiffs again cite **Delaney, 268 Kan. at 779, 999 P.2d at 938-39.** In that case the Kansas Supreme Court declined to apply K.S.A. § 60-3305 to manufacturing and design defect [**74] claims because to do so would restrict plaintiffs' abilities to recover for dangers which are open and obvious. Plaintiffs also cite **Green v. Smith & Nephew AHP, Inc., 2001 WI 109, 629 N.W.2d 727, 743, 245 Wis. 2d 772 (Wis. 2001),** as evidence of a national [*1122] trend to re-emphasize consumer expectations in strict liability cases.

Plaintiffs' argument that Kansas has jettisoned the learned intermediary doctrine, or is about to do so, is without merit. [HN19] Since 1981 - when Section 60-3305 was enacted - Kansas courts have repeatedly applied the learned intermediary rule. See **Humes v. Clinton, 246 Kan. 590, 602, 792 P.2d 1032, 1040 (1990); see also Savina, 247 Kan. at 122, 795 P.2d at 928; Johnson v. American Cyanamid Co., 239 Kan. 279, 286, 718 P.2d 1318, 1324 (1986).** Federal courts applying Kansas law have done likewise. See, e.g., **Ralston v. Smith & Nephew Richards, Inc., 275 F.3d 965, 974 (10th Cir. 2001); Wright ex rel. Trust Co. Of Kansas v. Abbott Lab., Inc., 259 F.3d 1226, 1233-34 (10th Cir. 2001).**

Plaintiffs' final argument is that "despite his contrary protestations and affidavit, . . . testimony [**75] indicates that Dr. Geenens, in all likelihood, bought in - hook, line and sinker - to the subliminal Pfizer marketing message." n92 Plaintiffs' Misrepresentation Response (Doc. # 516) at 10. In particular, plaintiffs assert that "Pfizer knew that it could influence prescribing physicians specifically about the suicide-causing potential of Zoloft and other SSRI drugs in subtle ways, and that it formulated its marketing plan in a manner which would

capitalize on that knowledge." n93 Id. Plaintiffs have cited no evidence, however, which raises a genuine issue of material fact whether Dr. Geenens relied on subtle and subliminal marketing influences, unknown to even himself, which were fraudulent. Plaintiffs do not cite a single statement or representation which Pfizer arguably knew was false when it was made. Also, Dr. Geenens has unequivocally testified that he did not review any documentation which Pfizer representatives gave him n94 and said that if Pfizer gave him an article, "I will pick it apart . . . I'm not interested." n95 Dr. Geenens evidently knew that Pfizer was trying to influence him and took measures to guard against such influence. Plaintiffs cite no evidence that [**76] Dr. Geenens' testimony in this respect is untruthful; in fact, they admit that he does not read pharmaceutical marketing, advertising or promotional materials provided by any manufacturer [*1123] or contained in any scientific and medical articles and journals. n96 In the final analysis, because plaintiffs' position is unsupported by record evidence, it rests on nothing but the hope that a jury may refuse to believe Dr. Geenens. [HN20] Plaintiffs' hope that something may turn up at trial, or that the jury will disbelieve Dr. Geenens, is insufficient to survive summary judgment. See **Thompson v. Hubbard, 257 F.3d 896, 899 (8th Cir. 2001)** (plaintiffs may not stave off summary judgment armed with only hope that jury might disbelieve witnesses' testimony); see also **Corrugated Paper Products, Inc. v. Longview Fibre Co., 868 F.2d 908, 914 n.7 (7th Cir. 1989)** (mere anemic hope that information contradicting deposition testimony would be elicited under cross-examination at trial insufficient to withstand motion for summary judgment); **Natrona Serv., Inc. v. Continental Oil Co., 435 F. Supp. 99, 106 (D. Wyo. 1977)** (where plaintiffs have failed to turn up substantial [**77] evidence in support of their theory, and defendants have introduced evidence negating theory, unreasonable to assume trial would provide plaintiffs with any greater opportunity to prove their theory, especially when the most that can be hoped for is to discredit the defendants' witnesses at trial). In Samarah, the district court stated:

n92 Pfizer contends that plaintiffs are barred from making this argument since they did not do so in the Pretrial Order (Doc. # 171). It is well established that "the pretrial order

supercedes all pleadings and controls the subsequent course of the case." **Metzger v. City of Leawood, 144 F. Supp. 2d 1225, 1258 (D. Kan. 2001) (citing Steil v. Humana Kansas City, Inc., 124 F. Supp. 2d 660, 665 (D.Kan. 2000);** Fed. R. Civ. P. 16(e); and D. Kan. Rule 16.2(c)). The Court agrees that the pretrial order does not sufficiently articulate a viable claim for fraud. It also finds that plaintiffs' claim is not well taken on the merits.

Pfizer also contends that when the Court ruled on Defendant Pfizer Inc.'s Motion *In Limine* No. 13 To Exclude All Zoloft Promotional, Marketing, Advertising And Sales Training Materials (Doc. # 272) filed April 28, 2000, it rejected plaintiffs' theory of "subliminal reliance " In its ruling, the Court held that because they were irrelevant and unfairly prejudicial, marketing materials that Dr. Geenens had not seen would not be admitted at trial. See Minute Sheet (Doc. # 500) filed September 5, 2001. This ruling does not necessarily bar plaintiffs from making a "subtle influence" argument, however, based on documents which Dr. Geenens did receive from Pfizer. [**78]

n93 Of course, to prove fraud, plaintiffs must also prove that the representations by Pfizer were known to be false at the time they were made. See **Smith v. Stephens, 23 Kan. App. 2d 1013, 1015, 940 P.2d 68, 69 (1997).**

n94 See Geenens Deposition (Exhibit G) in Pfizer's Marketing Defect Appendix (Doc. # 212) at 79 (throws pamphlets in "file 13" after representatives leave), 178:1-8 (does not review Pfizer pamphlets), 178-79 (does not read Pfizer promotions or advertisements).

n95 **Id. at 131:22-25.**

n96 Plaintiffs' Misrepresentation Response (Doc. # 516) at 5 (admitting Pfizer's uncontroverted facts that "When Dr. Geenens receives marketing, advertising or promotional materials for drugs, he immediately throws them into the trash can and does not read them" and that "similarly, Dr. Geenens does not read marketing, advertising or promotional materials

concerning drugs contained in the scientific and medical journals he reads".

. . . Dr. Poole's deposition testimony indicates that, in each case, his decision to use pedicle screws was made after considering [**79] the information contained in the relevant medical literature, the factual circumstances underlying each particular patient's medical condition, and his own medical judgment. There is simply no evidence in the record to support the allegation that Dr. Poole relied on any representations, fraudulent or otherwise, regarding the TSRH device's suitability for use in spinal fusion surgery. Absent any such proof, plaintiff cannot establish the element of reliance necessary for recovery on his claim for fraud, and summary judgment in favor of defendants with respect to plaintiff's fraud-based claims is therefore appropriate.

70 F. Supp. at 1209.; see also In re Orthopedic Bone Screw Litigation, 1999 U.S. Dist. LEXIS 4495, Nos. 3-96-1095, 4-96-1160, 3-96-1094, 3-96-1090, 4-96-1157, 97-1137, 3-96-1098, 1999 WL 628688,at *14-15 (D. Minn. Mar. 8, 1999) [HN21] (summary judgment appropriate when plaintiffs presented no evidence that treating physicians were misled by seminars or promotions or that they relied on defendants' representations to plaintiffs' detriment); **Greiner v. Sofamor, 1999 U.S. Dist. LEXIS 4484, No. 4-95-645, 1999 WL 716891,** at *4-5 (D. Minn. Mar. 8, 1999). Pfizer is therefore entitled to [**80] summary judgment on plaintiffs' marketing defect and misrepresentation claim.

II. Defendant Pfizer Inc's Motion For Partial Summary Judgment On Plaintiffs' Failure To Warn Claim (Count II) (Doc. # 504)

Plaintiffs claim that Pfizer's package insert and marketing materials

. . . do not warn about the risk of "SSRI-induced" akathisia, do not warn about emotional blunting or disinhibition, do not warn about the risk of mania, hypomania and psychosis, do not warn about the "serotonin syndrome," and do not warn that these

physical reactions to the drug can cause some people to act in violent or suicidal ways, or, indeed, that there is an increased risk of suicide caused by this drug at all. Nor are there any special and appropriate words of caution or warning about [*1124] the administration of Zoloft to children and adolescents.

Pretrial Order (Doc. # 171) at 3-4. Pfizer seeks summary judgment on plaintiffs' failure to warn claim, alleging that as a matter of law (1) plaintiffs cannot establish that Zoloft caused Matthew's death (general causation); (2) the record contains no evidence that a different or alternate warning would have changed Dr. Geenens' decision to prescribe [**81] Zoloft to Matthew (proximate causation); (3) the package inserts which Pfizer provided to Dr. Geenens in July 1997 were adequate and contained the very information which plaintiffs complain had been omitted; and (4) plaintiffs do not have expert testimony to support their warning claim. n97 The Court will first address Pfizer's arguments as to general and proximate causation.

n97 Plaintiffs' Count II is actually for both failure to warn and failure to test. See Amended Complaint (Doc. # 108) and Pretrial Order (Doc. # 171). In their response to Pfizer's motion, however, plaintiffs concede that "the duty to warn and the duty to test are, for all practical purposes, coextensive." Plaintiffs' Brief In Support Of Responses To Pfizer's Motions For Summary Judgment On Failure To Warn And Failure To Test Theories ("Plaintiffs' Failure To Warn Response") (Doc. # 515) filed October 3, 2001 at 11-12 (citing **Richter v. Limax Int'l, Inc., 45 F.3d 1464, 1467 (10th Cir. 1995)** (" [HN22] Manufacturers do not have a duty to test for inconceivable dangers, nor do they have a duty to test for every conceivable danger. They do have a duty to warn of dangers of harmful effects arising from the foreseeable use and misuse of a product that are known or are readily foreseeable in the state of art."); **Lindquist v. Ayerst Labs. Inc., 227 Kan. 308, 320, 607 P.2d 1339, 1350 (1980)** (any obligation to test is part of the duty to act in manner "reasonably necessary to secure the production of a safe product." (internal quotations omitted)); PIK-Civil 3rd § 128.04 commentary and cited cases). Previously, Pfizer had sought summary judgment on plaintiffs' failure to test claim; it

withdrew that motion during a telephone hearing with the Court on September 5, 2001. See Motion For Summary Judgment On Plaintiffs' Failure To Test Claim (Doc. # 215) filed April 18, 2000; Minute Sheet (Doc. # 500). Based on plaintiffs' response to its failure to warn motion, Pfizer asserts that plaintiffs have conceded that there is no separate and independent duty to test under Kansas law and therefore plaintiffs have effectively abandoned that claim. Because the parties appear to agree on this point, the Court will only analyze plaintiffs' claim as one for failure to warn.

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Preliminarily, the Court notes that plaintiffs' failure to warn claim involves three issues as to causation: (1) general causation, i.e. does Zoloft cause depressed patients to commit suicide; (2) specific causation, i.e. did Matthew Miller commit suicide because of Zoloft or for some other reason; and (3) proximate causation; i.e. whether Dr. Geenens would have prescribed Zoloft for Matthew if he had received adequate warning of the danger of Zoloft-induced suicide. Plaintiffs' arguments on causation are sometimes confusing because while they purport to address the question of specific causation - and in fact they seek summary judgment on that issue - they are actually addressing the question of proximate causation (and claiming that Pfizer bears the burden of proof on that issue). Plaintiffs admit that if the jury finds that Zoloft was not the cause of Matthew's suicide - an issue which incorporates both general and specific causation - "the question of whether Pfizer had a duty to warn about Zoloft-induced suicide will be irrelevant." n98 The Court therefore understands plaintiffs' arguments on causation to relate only to proximate causation and addresses them only [**83] in that context.

A. General Causation

Pfizer's first argument is that plaintiffs' claim must fail because they [*1125] have no proof of general causation. n99 Under [HN23] Kansas law, regardless of the theory upon which recovery is sought for injury in a products liability case, proof that a product defect caused the injury is a prerequisite to

recovery. See **Wilcheck v. Doonan Truck & Equip., Inc., 220 Kan. 230, 235, 552 P.2d 938, 942 (1976); Samarah, 70 F. Supp. 2d at 1202.** In the case of failure to warn, plaintiffs must produce evidence that Zoloft causes the behavior of which they complain, at least in some people. See **Smith v. Pfizer, 2001 U.S. Dist. LEXIS 12983, No. 98-4156, 2001 WL 968369,** at *7 (D. Kan. Aug. 14, 2001) (plaintiff must show that Zoloft can cause adverse reaction in order to prevail on failure to warn claim). Unfortunately, suicidality (including ideation, attempts and completed suicides) is a leading public health problem. See **Washington v. Glucksberg, 521 U.S. 702, 730, 138 L. Ed. 2d 772, 117 S. Ct. 2258 (1997).** It occurs in many people who are not exposed to Zoloft (or any other medicine). On the other hand, many people who are exposed [**84] to Zoloft do not become suicidal. Plaintiffs therefore cannot meet their burden of proving medical causation without expert testimony that Zoloft more likely than not caused Matthew's suicide. See **In re Breast Implant Litig., 11 F. Supp. 2d 1217, 1225-26 (D. Colo. 1998)** (because plaintiffs' injuries occur commonly in women without breast implants, plaintiffs must present expert testimony that exposure to breast implants more than doubled risk of alleged injuries); **Bacon v. Mercy Hosp., 243 Kan. 303, 307, 756 P.2d 416, 420 (1988)** (unless lack of reasonable care or existence of proximate cause is apparent to average layman from common knowledge or experience, expert testimony required to establish causation); see also **Dodge v. Cotter Corp., 203 F.3d 1190, 1200 n.12 (10th Cir. 2000)** (given novelty of medical causation theory linking exposure to molybdenum with osteoarthritis and bony extoses, essential that expert testimony is relevant and reliable and particular opinion based on valid reasoning and methodology); **Renaud v. Martin Marietta Corp., 972 F.2d 304, 307 (10th Cir. 1992)** (summary judgment proper where plaintiff [**85] failed to present sufficiently reliable epidemiological evidence that effluents in defendants' water system caused cancer and seizures); **Allison v. McGhan Medical Corp., 184 F.3d 1300, 1320 (11th Cir. 1999)** (medical expert testimony essential to prove causation; summary judgment properly granted where plaintiffs' medical expert testimony inadmissible); **Rosen v. Ciba-Geigy Corp., 78 F.3d 316, 319 (7th Cir. 1996)** (summary judgment properly granted where plaintiff failed to present admissible expert testimony that

nicotine patch caused heart attack; courtroom is not place for scientific guesswork, even of the inspired sort); **Daubert v. Merrell Dow Pharms., Inc., 43 F.3d 1311 (9th Cir. 1995)** (summary judgment affirmed where plaintiffs failed to present admissible evidence that use of bendectin caused birth defects).

n98 Plaintiffs' Brief In Support Of Refiled Motion For Partial Summary Judgment (Doc. # 524) filed October 23, 2001.

n99 See Memorandum In Support Of Motion For Summary Judgment On Plaintiffs' Failure To Warn Claim ("Pfizer's Failure To Warn Memorandum") (Doc. # 504) filed September 12, 2001 at 29.

[**86]

To support their claim of general causation, plaintiffs have relied exclusively on the testimony of Dr. Healy - their liability expert on that issue. The Court, however, has excluded Dr. Healy's testimony on that subject. See Memorandum And Order (Doc. # 559) filed February 8, 2001. Because plaintiffs have no scientific evidence of general causation, their claim of failure to warn must fail as a matter of law. n100

n100 To the extent plaintiffs may argue that Pfizer bears the burden of showing lack of general causation, they are clearly incorrect. In the cases which plaintiffs cite, plaintiff either retained the burden of proving general causation, see **Mason v. Texaco, Inc., 741 F. Supp. 1472, 1478-79 (D. Kan. 1990), Arnold v. Riddell, Inc., 882 F. Supp. 979, 989 (D. Kan. 1995),** and **Wooderson v. Ortho Pharm. Corp., 235 Kan. 387, 393-99, 681 P.2d 1038, 1045-48 (1984),** or general causation was not at issue, see **Meyerhoff v. Michelin Tire Corp., 852 F. Supp. 933, 936 (D. Kan. 1994).** In short, plaintiffs have no legal support for the proposition that Pfizer bears the burden of proof that Zoloft does not cause suicide through the mechanism of akathisia. Plaintiffs' logic in this regard is so circular as to be self-evidently flawed. Plaintiffs admit that before the burden would shift to Pfizer, they would be required to prove that the

warnings which Pfizer gave were illegal or inadequate to advise them of the risk that Zoloft causes suicide through akathisia in some depressed patients. Even under their theory, in order to satisfy their burden of proof, plaintiffs would necessarily have to prove some degree of general causation - either that there was "reasonable evidence of a serious hazard" with Zoloft, under **21 C.F.R. § 201.57(e)**, or that the drug had "dangerous propensities." **Wooderson, 235 Kan. at 401, 681 P.2d 1050.**

[*1126]

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B. Proximate Causation

Pfizer also argues that it is entitled to summary judgment because plaintiffs cannot show that an failure to warn proximately caused Matthew's death. Plaintiffs' initial response is that they do not bear the burden of proof on this issue - Pfizer does. Plaintiffs' argument is that "if the Court holds or the jury finds that Pfizer violated federal warnings, regulations or its common law duty to warn/test, then the presumption of causation switches the burden of proof to Pfizer." n101 Pfizer argues that Kansas law does not permit, much less require, such burden-shifting.

n101 Plaintiffs' Failure To Warn Response (Doc. # 515) at 11-12

[HN24] In order to survive summary judgment, plaintiffs must provide evidence that a failure to warn proximately caused Matthew's death. See **Wooderson, 235 Kan. at 409, 681 P.2d at 1057; see also Eck v. Parke, Davis & Co., 256 F.3d 1013, 1018 (10th Cir. 2001) (citing Mazur v. Merck & Co., 742 F. Supp. 239, 262 (E.D. Pa. 1990)).** [**88] Plaintiffs are correct that [HN25] Kansas law allows a rebuttable presumption of causation once plaintiffs have established that a warning is inadequate. If plaintiffs prove that Pfizer failed to provide a proper warning, Kansas law presumes that a doctor would have heeded a proper warning. See **Wooderson, 235 Kan. at 407,**

681 P.2d at 1057. Essentially, the law presumes that but for the inadequate warning, the patient would not have been harmed, since the doctor would have given the patient an adequate warning if she or he had ever received it, and the inadequate warning is therefore the cause of the patient's injury. See **Wooderson, 235 Kan. at 409, 681 P.2d at 1057; Arnold, 882 F. Supp. at 996; Meyerhoff, 852 F. Supp. at 946-47;** n102 **Mason,** [*1127] **741 F. Supp. at 1490.** Defendant may rebut this presumption by establishing that although the prescribing physician would have read and heeded the warning or additional information, this would not have changed his or her course of treatment. See **Eck, 256 F.3d at 1019.** If Pfizer provides credible evidence to rebut the presumption, the presumption disappears [**89] and the burden shifts back to plaintiffs to affirmatively prove causation. See id.; **Woulfe v. Eli Lilly & Co., 965 F. Supp. 1478, 1483 (E.D. Okla. 1997).**

n102 Plaintiffs cite Meyerhoff for the proposition that the presumption of causation is essentially irrebuttable until trial. In Meyerhoff, however, the district court did not hold that the presumption was irrebuttable; rather, it found that defendant had failed to put forth sufficient evidence to rebut it. Ultimately, defendant's motion for a judgment as a matter of law was granted when plaintiff produced insufficient evidence at trial that defendant could have designed a better warning. See 852 F. Supp. at 947-48.

Plaintiffs also rely on **Dole Food Co. v. North Carolina Foam Indus., 188 Ariz. 298, 935 P.2d 876, 883-84 (Ariz. Ct. App. 1996),** which held that a presumption of causation survived defendant's contrary evidence. In that case, however, the court found that "a reasonable jury could still infer that [plaintiff] would have heeded adequate warnings because [defendant's] evidence did not show that [plaintiff] received clear and adequate warnings." Id. The Court did not hold that the presumption never dissipates, merely that defendant had failed to rebut the presumption in that case. See id.

Plaintiff also cites K.S.A. § 60-414 for the proposition that the presumption permanently shifts the burden of proof of

proximate causation to defendant. [HN26] Section 60-414 does establish two kinds of presumptions, those that permanently shift the burden of proof when plaintiff has put forth facts that have any probative value as evidence of the existence of the presumed fact, and those that disappear if the facts from which the presumption arises have no probative value as evidence of the presumed fact. In this case, plaintiffs' evidence regarding the alleged inadequacy of Pfizer's warning does not have any probative value as to whether Dr. Geenens knew about the risk of Zoloft-induced suicide. The presumption is therefore in the first category and disappears when Pfizer puts forth contrary evidence.

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To submit the case to a jury, [plaintiff] must either discredit the physicians' testimony or call into question the substance of the testimony, or otherwise demonstrate that the alleged failure to warn was the proximate cause of their injuries. [HN27] Such a showing requires that the plaintiff "demonstrate that the additional non-disclosed risk was sufficiently high that it would have changed the treating physician's decision to prescribe the product for the plaintiff."

Eck, 256 F.3d at 1019. n103 Thus, once the presumption is rebutted, plaintiffs must further establish proximate causation by showing that had Pfizer issued a proper warning to the learned intermediary, he would have altered his behavior and the injury would have been avoided. **Id. at 1018.** To submit the case to a jury, plaintiffs must either discredit Dr. Geenens' testimony or call into question the substance of the testimony, or otherwise demonstrate that the alleged failure to warn was the proximate cause of their injuries. See id. Such a showing requires that plaintiff "demonstrate that the additional non-disclosed risk was sufficiently high that it would have changed the [**91] treating physician's decision to prescribe the product for the plaintiff." Id. As discussed below, plaintiffs have not met that burden.

n103 Eck is an Oklahoma case. As Pfizer points out, however, Oklahoma applies the same rebuttable presumption concerning warnings that Kansas utilizes.

The Court assumes without deciding that plaintiffs are entitled to the benefit of a presumption of causation. It also holds that Pfizer has successfully rebutted that presumption through Dr. Geenens' testimony that a different warning would not have mattered. n104 As noted above, Dr. [*1128] Geenens stated under oath that even if he had been provided the information and opinions expressed by Dr. Healy, and received plaintiffs' additional warnings, he would have prescribed Zoloft for Matthew without further warning or instructions. This testimony is uncontroverted, and it rebuts the presumption that Dr. Geenens would have altered his treatment decision if he had received additional warnings. See **Eck, 256 F.3d at 1020-21** [**92] (physician's testimony that she would not have changed her course of treatment even if she had known information plaintiff claimed she did not have was sufficient to rebut presumption).

n104 See Pfizer's Failure To Warn Memorandum (Doc. #) at 44 (citing **Eck, 256 F.3d at 1024).** Pfizer also cites a litany of cases from other circuits in support of this argument: **Odom v. G.D. Searle & Co., 979 F.2d 1001, 1003-04 (4th Cir. 1992)** (summary judgment appropriate where physician testified that different warning would not have changed his decision to prescribe device); **Willett v. Baxter Intern, Inc., 929 F.2d 1094, 1098-99 (5th Cir. 1991)** (failure to warn was not proximate cause of plaintiff's injury where only reasonable conclusion was that adequate warning would not have affected physician's decision to proceed with surgery); **Dyer v. Danek Med., Inc., 115 F. Supp. 2d 732, 742 (N.D. Tex. 2000)** (granting summary judgment where trier of fact would reasonably infer that physician's decision would have been unchanged even if warned); **Dyson v. Winfield, 113 F. Supp. 2d 35, 41 (D.D.C. 2000)** (granting defendant's motion for summary judgment); **Lawson v. Smith & Nephew Richards, Inc., 1999 U.S. Dist. LEXIS 18922, 1999 WL 1129677,** at *6

(N.D. Ga. 1999) ([HN28] where learned intermediary has actual knowledge of substance of alleged warning and would have taken same course of action even with information plaintiff contends should have been provided, courts typically conclude that learned intermediary doctrine applies or that causal link is broken and plaintiff cannot recover); **Talley v. Danek Med., Inc., 7 F. Supp. 2d 725, 730 (E.D. Va. 1998)** (plaintiff must not only show that manufacturer's warning was inadequate but that such inadequacy affected physician's use of product and thereby injured plaintiff), aff'd, **179 F.3d 154 (4th Cir. 1999); In Re Norplant Contraceptive Prods. Liab. Litig., 955 F. Supp. 700, 710-11 (E.D. Tex. 1997)** (granting summary judgment where physicians testified unequivocally that no information plaintiffs alleged should have been provided would have changed their minds about whether to prescribe drug at issue), aff'd, **165 F.3d 374 (5th Cir. 1999); Chambers v. G.D. Searle & Co., 441 F. Supp. 377, 384 (D. Md. 1975)** (granting motion for directed verdict where as result of what physician knew and conclusions he drew from what he knew, it would have made no difference if warnings were in form which plaintiff contends would be adequate), aff'd, **567 F.2d 269 (4th Cir. 1977).**

[**93]

Woulfe, 965 F. Supp. at 1478, is instructive on this point. n105 There, plaintiff claimed that Eli Lilly's failure to warn about the risk of Prozac-induced suicide had caused or contributed to his father's death. **Id. at 1479.** The district court found that even if Eli Lilly's warning was inadequate, even though Oklahoma "embraces a rebuttable presumption that an adequate warning would have been read and heeded," Eli Lilly had successfully rebutted the presumption by offering the undisputed testimony from the prescribing physician that he would have prescribed Prozac even if the labeling had contained plaintiff's suggested warning. **Id. at 1482, 1486 (citing Daniel v. Ben E. Keith, Co., 97 F.3d 1329 (10th Cir. 1996)).** In an affidavit, the treating physician testified that he was aware of the information which Eli Lilly provided in the PDR and that even if the package insert had contained plaintiff's proposed warning, he would have prescribed Prozac. See 965 F. Supp. at 1481.

n105 Plaintiffs point out that Woulfe settled on appeal and imply that the Tenth Circuit would have reversed the district court's holding, but this argument is pure speculation.

[**94]

Similarly in this case, Dr. Geenens' testimony rebuts the presumption that a different warning would have altered his treatment decision. The Court's inquiry then looks to whether plaintiffs have come forward with evidence sufficient to submit the case to a jury to determine whether inadequate warnings were a proximate cause of Matthew's injuries. See Eck 256 F.3d at 1019 (citing **Woulfe, 965 F. Supp. at 1483; Garside v. Osco Drug, Inc., 976 F.2d 77, 81 (1st Cir. 1992)** n106). As noted, Dr. Geenens' testimony [*1129] is unrefuted, and in this case plaintiffs have not raised a genuine issue of material fact that would cause a reasonable jury to discredit it. This is particularly true because (1) plaintiffs have not proposed a specific warning which might have more clearly communicated to Dr. Geenens the risks of which they complain; (2) plaintiffs have not shown that the warning improvements which they generally sponsor would have been material to the treatment decisions of reasonable physicians or to Dr. Geenens in particular; and (3) Dr. Geenens was already well aware of the information which plaintiffs claim Pfizer should have supplied. n107 No reasonable jury [**95] comparing the Zoloft package insert against plaintiffs' allegations that Pfizer did not warn about the risk of SSRI-induced akathisia, emotional blunting, disinhibition, mania, hypomania, psychosis, serotonin syndrome and violent or suicidal behavior, would find that Dr. Geenens is lying when he says that additional warnings were not necessary and would not have changed his decision to prescribe Zoloft to Matthew. n108

n106 Plaintiffs rely heavily on **Garside, 976 F.2d at 77,** in which the First Circuit held that "a physician's statement about what s/he would have done in the face of an adequate warning raises a credibility issue which must be decided by a jury." See **id. at 83 n.9.** In that case, the affidavit of the treating physician showed that he knew of a connection between the drug

and the adverse reaction at the time of his affidavit in (1989), but not at the time of the injury (in 1982). **976 F.2d at 82.** Based on the non-conclusive nature of this testimony, the First Circuit reversed the entry of summary judgment in favor of the drug manufacturer. See **id. at 82 (citing Stanback v. Parke, Davis & Co., 657 F.2d 642, 645 (4th Cir. 1981)** (holding that warning about risk of acquiring neurological disorder from ingesting drug would not have altered physician's behavior where his decisions and actions were made in full knowledge of that information)). Here, however, Dr. Geenens has unequivocally sworn that "at the time I prescribed Zoloft for Matthew Miller, I knew published case reports and adverse-event reports to the FDA had described instances of patients reporting suicidal ideation and attempting or committing suicide while undergoing psychotherapy treatment, which included the use of selective serotonin reuptake inhibitors." Geenens Affidavit (Exhibit A) in Reply In Support Of Pfizer's Motion For Partial Summary Judgment On Plaintiffs' Failure To Warn Claim ("Pfizer's Failure To Warn Reply") (Doc. # 518) filed October 15, 2001 at P9. [**96]

n107 Dr. Geenens reviewed selected pages of Dr. Healy's deposition testimony, Dr. Healy's expert reports of August 13 and December 10, 1999 and March 6, 2000 (including Dr. Healy's article on Zoloft And Suicide: Causal Mechanisms), the Hindmarch Study, and Dr. Healy's article titled Emergence Of Antidepressant Induced Suicidality. Dr. Geenens swore that none of these documents caused him to believe that he was uninformed or misinformed of any clinically significant risk that would have affected his treatment of Matthew in June and July 1997. Furthermore, Dr. Geenens swore that even if he had seen those specific materials before July 21, 1997, he would have prescribed Zoloft 50 mg. for Matthew because it was his medical judgment that it was in Matthew's best interest. See Geenens Affidavit (Exhibit A) in Pfizer's Failure To Warn Reply (Doc. # 518) at PP8, 15.

n108 In so holding, the Court does not disregard the possible bias in Dr. Geenens' testimony arising from his business relationship with Pfizer, i.e. the fact that at or near the time he

prescribed Zoloft for Matthew, Dr. Geenens was a paid consultant for Pfizer. Rather, the Court holds that no reasonable jury would discredit his testimony - which is not refuted by any direct of circumstantial evidence - on that ground alone. Plaintiffs' attack on Dr. Geenens' credibility does not create a genuine issue of material fact. See, e.g., **Eck, 256 F.3d at 1024** (credibility challenge purely speculative and "clearly insufficient" to call into question either credibility of doctor or veracity of her statement when plaintiff challenged doctor's motives and noted that doctor had previously conducted research for pharmaceutical companies); **Talley, 179 F.3d at 164** (rejecting claim that learned intermediary doctrine should not apply where prescribing physician was consultant to defendant, taught surgical procedures as part of that arrangement and received annual consulting fee of $ 250,000, a travel budget, research funds and 25,000 stock shares; "no evidence that the consulting relationship between Dr. Matthews and Danek interfered with Dr. Matthew's independent medical judgment in treating Talley").

n109

n109 See Pfizer's Failure To Warn Memorandum (Doc. # 504) at 47.

[**97]

Plaintiffs take specific issue with this view of the record, citing the following deposition testimony by Dr. Geenens: n110

Q. You would heed any warning that the drug manufacturer gave you about risks of their drug, wouldn't you?

A. I would consider that in my clinical decision-making.

Q. Well, can you give me any circumstance in which you in your clinical decision-making would ignore a bold-faced warning in the package insert for a psychoactive drug?

A. Bold print black box is information that I would incorporate into my clinical decision-making.

Q. Dr. Geenens, I won't quibble with you. I just want to know if there is any circumstance you can evision where you [*1130] would ignore or fail to heed a bold-faced warning about a drug?

A. I would do my absolute best to heed that type of warning.

n110 Geenens Deposition (Exhibit 1) in Plaintiffs' Ex., Vol. I (Doc. # 525) at 89-91.

Plaintiffs argue that Dr. Geenens' testimony does not unequivocally show what he would have done [**98] if he had a bold print black box warning in front of him at the time that he prescribed Zoloft for Matthew. To some degree, plaintiffs also argue that if Dr. Geenens had actually seen their proffered information in a package insert, rather than in the form of deposition testimony by Dr. Healy, he would have heeded that warning. As Pfizer points out, however, the "Adverse Reactions" section of the package insert contained information regarding suicidal ideation and attempts during clinical trials and Dr. Geenens clearly swore that he was aware of this information and that further warnings would not have affected his treatment decision.

[HN29] When the FDA discovers special problems, particularly those that may lead to death or serious injury, it may require a drug manufacturer to place a warning about that problem in a prominently displayed box. n111 If a boxed warning is required, the FDA will specify its location. n112 The record is devoid of any evidence that the FDA would have approved a black box warning that Zoloft may cause suicide, however, and plaintiffs have not specifically argued that a black box warning was appropriate or suggested what a black box warning might say. Plaintiffs [**99] are therefore in no position to fault the "equivocal" nature of Dr. Geenens' testimony about what weight he might have afforded a hypothetical bold print black box warning. Furthermore, Dr. Geenens knew about the very risks which plaintiffs would apparently put a black box warning and

they are already contained elsewhere in the package insert, in the "Precautions" and "Adverse Reactions" sections. Here, as in **Woulfe, 965 F. Supp. at 1484,** plaintiffs seem to simply argue that a jury could disbelieve the testimony of Dr. Geenens and that this possibility is sufficient to defeat an otherwise well-taken motion for summary judgment. That, however, is not the law.

n111 **21 C.F.R. § 201.57(e).**

n112 **Id.**

In summary, plaintiffs have not raised a general issue of material fact with regard to proximate causation. Since Dr. Geenens' unequivocal testimony breaks the causal chain as to allegedly inadequate warnings, summary judgment for Pfizer is appropriate and Pfizer [**100] is entitled to summary judgment on plaintiffs' failure to warn claim. n113

n113 Because the Court finds that Pfizer's first two arguments have merit, it need not address Pfizer's contentions that the warning which was in effect during July 1997 was reasonable as a matter of law and that plaintiffs do not have admissible expert testimony on the subject of warnings.

III. Plaintiffs' Summary Judgment Motion (Doc. # 523)

Plaintiffs initially filed their motion for summary judgment on April 18, 2000, alleging that they were entitled to summary judgment on their claim that Pfizer (1) failed to adequately warn about the potential dangers of suicide associated with Zoloft and the use of Zoloft for depressed children and adolescents; and (2) failed to conduct reasonable tests and investigations regarding the potential causal relationship between Zoloft and suicide. n114 On September 14, 2001, the Court allowed plaintiffs to withdraw their summary judgment motion and gave them leave to refile it by October 1, 2001. n115 [**101] More than three weeks out of [*1131] time, on October 23, 2001, plaintiffs refiled their motion for summary judgment. n116 Even though

the Court might strike plaintiffs' motion because it was not timely filed, the Court need not do that because the motion is both moot and lacking in merit. All of plaintiffs' arguments have been addressed elsewhere.

n114 See Plaintiffs' Motion For Partial Summary Judgment (Doc. # 204).

n115 See Minute Sheet (Doc. # 509).

n116 See Plaintiffs' Motion For Partial Summary Judgment (Doc. # 523).

IV. Motion In Limine (Doc. # 276)

Pfizer has a pending motion in limine in this matter: Defendant Pfizer Inc.'s Motion In Limine No. 15 To Exclude References To Its Financial Condition And Announced Merger (Doc. # 276) filed April 28, 2000. Because the Court has granted Pfizer's summary judgment motions on both of plaintiffs' claims, the motion in limine is overruled as moot.

IT IS THEREFORE ORDERED that Defendant Pfizer Inc's Motion For Partial Summary Judgment [**102] On Plaintiffs' Claim Of Marketing Defect And Misrepresentation (Doc. # 505) filed September 12, 2001 be and hereby is SUSTAINED.

IT IS FURTHER ORDERED that Defendant Pfizer Inc's Motion For Partial Summary Judgment On Plaintiffs' Failure To Warn Claim (Doc. # 504) filed September 12, 2001 be and hereby is SUSTAINED.

IT IS FURTHER ORDERED that Plaintiffs' Motion For Partial Summary Judgment (Doc. # 523) filed October 23, 2001 be and hereby is OVERRULED.

IT IS FURTHER ORDERED that Defendant Pfizer Inc.'s Motion In Limine No. 15 To Exclude References To Its Financial Condition And Announced Merger (Doc. # 276) filed April 28, 2000 be and hereby is OVERRULED as moot.

IT IS FURTHER ORDERED that the Clerk of the Court send copies of this Memorandum and Order to the Court-Appointed experts, in addition to counsel of record:

John M. Davis, M.D.

University of Illinois at Chicago

Department of Psychiatry

UIC 912 South Wood Street

Chicago, IL 60612

John Concato, M.D., M.S., M.P.H.

Yale University School of Medicine

333 Cedar Street; SHM IE-61

New Haven, CT 06510.

Dated this 11th day of February, 2002 at Kansas [**103] City, Kansas.

Kathryn H. Vratil

United States District Judge

LEXSEE 356 F. 3D 1326

MARK MILLER, individually and as administrator of the estate of Matthew Miller, deceased; CHERYL MILLER, individually, Plaintiffs-Appellants, v. PFIZER, INC., Roerig Division, Defendant-Appellee.

No. 02-3092

UNITED STATES COURT OF APPEALS FOR THE TENTH CIRCUIT

356 F.3d 1326; 2004 U.S. App. LEXIS 1711

February 4, 2004, Filed

PRIOR HISTORY: [**1] APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF KANSAS. (D.C. NO. 99-CV-2326-KHV). Miller v. Pfizer Inc., 196 F. Supp. 2d 1095, 2002 U.S. Dist. LEXIS 2388 (D. Kan., 2002) Miller v. Pfizer Inc., 196 F. Supp. 2d 1062, 2002 U.S. Dist. LEXIS 2298 (D. Kan., 2002)

DISPOSITION: Affirmed. Defendant's Motion to Strike granted. Defendant's Motion to Take Judicial Notice and Plaintiffs' Requests for Judicial Notice denied.

CASE SUMMARY:

PROCEDURAL POSTURE: The United States District Court for the District of Kansas granted summary judgment to appellee drug manufacturer after appellant parents filed a wrongful death action against the drug manufacturer following the death of their son, who committed suicide one week after he started taking the drug it made to treat depression. The parents appealed.

OVERVIEW: A doctor prescribed the drug manufacturer's drug to treat the depression of the parents' 13-year-old son. One week later, the son hanged himself. The parents filed a wrongful death suit against the drug manufacturer. They retained an expert witness. The expert opined that the drug caused a syndrome which caused some patients to commit suicide. In forming his

opinion, the expert relied on various articles, studies, and related material. The expert filed a report about his conclusions. The trial court appointed two independent experts who studied various materials, including the opinions of the parents' expert. They submitted a report that generally discredited the expert's theory and methodology. At a hearing, the trial court restricted the information the independent experts could rely on. It then declined to allow the expert to testify at trial and granted summary judgment to the drug manufacturer. On appeal, the appellate court found that the trial court did not abuse its discretion in restricting the information made available to the independent experts, did not err in excluding the expert's testimony, and did not err in granting summary judgment to the drug manufacturer.

OUTCOME: The trial court's judgment was affirmed.

LexisNexis (TM) HEADNOTES - Core Concepts:

Evidence > Procedural Considerations > Rulings on EvidenceEvidence > Witnesses > Expert Testimony
[HN1] The four Daubert factors relevant to the determination of whether a proffered expert's proposed testimony reflects scientific knowledge that will assist the trier of fact to resolve a fact in issue are: (1) whether the scientific theory or technique can and has been tested, (2) whether the theory or technique has been subjected to peer review and publication, (3) the known or potential rate of error of the technique, and (4) whether the methodology has attained general acceptance in the scientific community.

Civil Procedure > Disclosure & Discovery > Mandatory DisclosuresCivil Procedure > Discovery Methods > Expert Witness Discovery
[HN2] See Fed. R. Civ. P. 26(a)(2).

Civil Procedure > Disclosure & Discovery > Mandatory Disclosures
[HN3] Supplemental disclosures are permitted, and indeed may be required. Fed. R. Civ. P. 26(e). Such supplements are to be

disclosed by the time pretrial disclosures are due under Fed. R. Civ. P. 26(a)(3). Fed. R. Civ. P. 26(e).

Civil Procedure > Disclosure & Discovery > Mandatory Disclosures

[HN4] A party that without substantial justification fails to disclose information required by Fed. R. Civ. P. 26(a) or Fed. R. Civ. P. 26(e)(1) is not, unless such failure is harmless, permitted to use as evidence at a trial, at a hearing, or on a motion any witness or information not so disclosed.

Civil Procedure > Disclosure & Discovery > Mandatory DisclosuresEvidence > Procedural Considerations > Rulings on EvidenceEvidence > Witnesses > Expert Testimony

[HN5] A court's failure to permit the reports of experts to be supplemented can constitute an abuse of discretion in some circumstances. Trial courts may abuse their discretion when deciding whether to admit expert testimony by unreasonably limiting the evidence upon which to base a decision.

Civil Procedure > Disclosure & Discovery > Mandatory Disclosures

[HN6] The orderly conduct of litigation demands that expert opinions reach closure. Scientific conclusions are subject to perpetual revision. Law, on the other hand, must resolve disputes finally and quickly.

Civil Procedure > Disclosure & Discovery > Mandatory DisclosuresEvidence > Procedural Considerations > Rulings on Evidence

[HN7] Under Fed. R. Civ. P. 1, the civil procedure rules shall be construed and administered to secure the just, speedy, and inexpensive determination of every action.

Civil Procedure > Appeals > Standards of Review > De Novo ReviewCivil Procedure > Appeals > Standards of Review > Abuse of DiscretionEvidence > Procedural Considerations > Rulings on EvidenceEvidence > Witnesses > Expert Testimony

[HN8] A reviewing court reviews de novo the question of whether a trial court performed its gatekeeper role and applied the proper legal standard in admitting an expert's testimony. It

then reviews for abuse of discretion the trial court's actual application of the gatekeeper standard in deciding whether to admit or exclude an expert's testimony.

Evidence > Procedural Considerations > Rulings on EvidenceEvidence > Witnesses > Expert Testimony
[HN9] The analysis outlined in Daubert is extensive, requiring the trial court to carefully and meticulously review the proffered scientific evidence.

Civil Procedure > Appeals > Reviewability > Preservation for ReviewCivil Procedure > Appeals > Briefs
[HN10] A reviewing court need not address an argument where a party did not raise it in the party's appellate briefs.

Civil Procedure > Appeals > Reviewability > Preservation for Review
[HN11] A reviewing court need not consider an argument made for the first time on appeal.

COUNSEL: Arnold Anderson Vickery, Houston, Texas (James E. Fitzgerald, Cheyenne, Wyoming, and Earl Landers Vickery, Austin, Texas, with him on the briefs), for Plaintiffs-Appellants.

Malcolm E. Wheeler (James E. Hooper, Amy L. Padden and Craig R. May, with him on the brief), of Wheeler Trigg & Kennedy, P.C., Denver, Colorado, for Defendant-Appellee.

JUDGES: Before EBEL, ANDERSON, and HARTZ, Circuit Judges.

OPINIONBY: [*1327] Hartz

OPINION: HARTZ, Circuit Judge.

Matthew Miller died at the age of thirteen, one week after beginning to take sertraline, an antidepressant drug marketed as "Zoloft." His parents sued Pfizer, the manufacturer of Zoloft, for wrongful death, claiming that Zoloft caused Matthew to commit suicide.

The Millers hired Dr. David Healy, who proposed to testify that Zoloft may cause suicide and had in fact caused Matthew to commit suicide. Applying standards outlined in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 125 L. Ed. 2d 469, 113 S. Ct. 2786 (1993), and its progeny for determining whether expert testimony is admissible under Federal Rule of Evidence 702 [**2] , the district court ruled that Dr. Healy could not testify. This left the Millers with no expert to provide evidence of causation. Accordingly, the court granted summary judgment to Pfizer.

The Millers appeal. Their principal claim is that the court did not give them a fair opportunity to make a proper record supporting Dr. Healy's conclusions. At the outset of discovery the Millers had requested the court to appoint independent experts to evaluate the opinions of the parties' retained experts. The district court did so only after completion of discovery. The court-appointed experts ultimately [*1328] advised the court that Dr. Healy's analysis was unscientific. The Millers now argue that the district court improperly deprived Dr. Healy of the opportunity to respond to concerns expressed by the independent experts. If the district court had indeed deprived Dr. Healy of that opportunity, the Millers might prevail on a claim of abuse of discretion. Our review of the record, however, establishes that the district court acted with patience and fairness. Most, if not all, of the concerns expressed by the independent experts had previously been expressed by Pfizer or the district court. The Millers [**3] have failed to identify any concern to which they lacked an adequate opportunity to respond. We exercise jurisdiction under 28 U.S.C. § 1291 and affirm.

I. BACKGROUND

Dr. Douglas Geenens diagnosed 13-year-old Matthew Miller with depression and prescribed Zoloft on July 21, 1997. Matthew hanged himself one week later. The Millers filed a wrongful death action against Pfizer in the United States District Court for the District of Kansas on July 27, 1999, basing federal jurisdiction on diversity of citizenship, *see* 28 U.S.C. § 1332. Their expert witness on causation has been Dr. David Healy, a neuropsychopharmacologist.

Zoloft belongs to a class of drugs called selective serotonin reuptake inhibitors (SSRIs). Dr. Healy asserts that SSRIs cause akathisia, a syndrome involving motor restlessness, which in turn causes some patients to commit suicide. In forming his opinion Dr. Healy relied on various articles and studies involving Zoloft and other SSRIs. Of these studies, he placed the most emphasis on his own healthy-volunteer study, two "challenge-dechallenge-rechallenge" reports (in which subjects were given the drug, then [**4] not given it, and then given it again), and a study conducted by Dr. Ian Hindmarch (although he ultimately decided not to rely on the Hindmarch study). He also relied on depositions from this case; testimony, depositions, and exhibits from other cases; Pfizer documents; an application of what are known as Koch's postulates (which are employed to evaluate causality); and a meta-analysis he performed using Pfizer data.

Shortly after bringing suit, the Millers submitted a preliminary report prepared by Dr. Healy. Anticipating that Dr. Healy's views might be challenged by Pfizer, the Millers, in an effort to obtain validation of Dr. Healy's opinions from an outside source, filed a motion to appoint independent experts on October 21, 1999.

The court's first scheduling order, entered November 18, 1999, required the Millers to provide Pfizer with their Rule 26 expert disclosures no later than December 28, 1999. The scheduling order also set a deadline of February 11, 2000, for the Millers to provide Rule 26 disclosures pertaining to rebuttal experts. On January 10, 2000, Pfizer filed a "Motion to Limit Revision, Amendment or Supplementation of Expert Opinions Disclosed Pursuant to Rule [**5] 26(a)(2)." The district court sustained this motion in part on January 28, 2000. It ruled that the Millers could "serve a supplemental final expert report on or before [March 7, 2000]," and final rebuttal expert disclosures by March 28, 2000. Dist. Ct. R., Doc. 115.

On March 27-28, 2000, Dr. Healy was deposed for ten hours. During the following two weeks the Millers provided Pfizer with supplemental responses to Pfizer's requests for admission. The responses contained an explanation of a

statistical analysis performed by Dr. Healy. Objecting to the responses as untimely, Pfizer filed on April 17, 2000, an "Emergency Motion to Bar Plaintiffs' Expert, Dr. Healy, from Supplementing His Opinions and to Strike and Deem Admitted Plaintiffs' Second [*1329] Supplemental Responses to First Requests for Admissions." Dist. Ct. R., Doc. # 195. The district court denied this motion on April 18, 2000, after observing that "the newly disclosed information does not appear to substantially depart from information which has been previously disclosed." Dist. Ct. R., Doc. # 199 at 2. But it reserved its final ruling on the issue until it considered the parties' dispositive motions and stated that it "may [**6] well strike Dr. Healy's information because of the late hour at which it has been produced." *Id.* at 2-3.

Also on April 18, 2000, Pfizer filed a motion to exclude Dr. Healy's testimony under *Daubert*. Proceedings were delayed, however, when Pfizer's attorney was seriously injured in an accident on June 2, 2000. The district court continued the trial date from July 18 to September 19, 2000. Then, on August 18, 2000, the district court issued an order staying all proceedings and directing the parties to show cause why independent expert witnesses should not be appointed. Ultimately, on April 24, 2001, the court entered an order appointing two independent experts, John Concato, M.D., M.S., M.P.H. and John M. Davis, M.D. In its order appointing the experts, the district court identified the "fundamental question" on which it wanted advice: "whether Dr. Healy's methodology, and his application of it in this case, constitute valid, scientifically reliable reasoning in support of his opinions that Zoloft causes suicide (general causation) and that Zoloft caused Matthew Miller's suicide (specific causation)." Aplt. App. at 359. The order declared that "the parties [had been] afforded [**7] full opportunity to adduce evidence in support of their respective positions." *Id.* It then stated that the independent experts would be provided "(1) a copy of the parties' previously filed briefs pertaining to the motion to exclude Dr. Healy's testimony; (2) a copy of all exhibits cited or referred to in those briefs . . .; (3) a copy of Pfizer's July 1999 Report to the Irish Medicines Board; (4) the letter of January 2000 from the Irish Medicines Board to Pfizer regarding the report; and (5) Dr. Healy's Declaration of August,

2000, which addresses the concerns which the Court articulated in its order to show cause." *Id.* at 360. The materials provided to the independent experts included various expressions of Dr. Healy's opinions as they had evolved during the course of the litigation: reports dated September 22 and December 10, 1999; a Letter Report dated March 6, 2000; deposition testimony on March 27-28, 2000; responses filed in April 2000 to Pfizer's requests for admission; and declarations dated May 9 and August 31, 2000. The district court also encouraged the experts "to examine whatever medical or scientific literature is necessary to render their professional opinions. [**8] " Aplt. App. at 361.

The independent experts submitted a report on September 5, 2001, that generally discredits Dr. Healy's theory and methodology. In response, the Millers filed a "Consolidated Statement of Facts" on October 23, 2001. *Id.* at 389. The court described it as a "45-page brief containing 145 separately numbered statements, 119 of which are presented for the first time in this document." Dist. Ct. Order (Nov. 16, 2001), Aplt. App. at 440. The district court granted Pfizer's motion to strike the statement on the grounds that it was not associated with any pending motion (or constituted an improper attempt by the Millers to supplement their summary-judgment briefing), did not comply with procedural rules, and was untimely.

On November 19-20, 2001, the district court held a hearing on the motion to exclude Dr. Healy's testimony as inadmissible [*1330] under *Daubert.* The court allowed Dr. Healy to engage in a dialogue with the independent experts but, apparently relying on Federal Rule of Civil Procedure 26, restricted the information on which his responses to their questions could be based to those materials that had previously been [**9] supplied to the independent experts. *See* Tr. of *Daubert* Hr'g, Aplt. App. at 592. The court explained:

"Under our federal rules which govern pretrial proceedings . . . there's a time set as part of the discovery process where each expert is required to produce a written report that states all of the opinions that . . . [the] expert will offer at the trial, and also the basis for the opinions. That has to be done by a certain time prior to trial. . . .

. . . To the extent that Dr. Healy had information and could have made calculations by that deadline, he was required to do that . . . ."

Id. In so limiting Dr. Healy, the court characterized his testimony as a "moving target" and declared that "the time for his expert opinions to be formulated and expressed and communicated to the other side is passed." *Id.* at 546. The Millers complain in particular that this ruling precluded Dr. Healy from presenting at the hearing some power-point slides that they contend would have addressed the concerns of the court-appointed experts.

Following the *Daubert* hearing the district court, largely adopting the views expressed by the independent experts, excluded [**10] Dr. Healy's testimony. The district court considered [HN1] four factors identified by the Supreme Court in *Daubert* as relevant to the determination of whether a proffered expert's proposed testimony reflects scientific knowledge that will assist the trier of fact to resolve a fact in issue: (1) whether the scientific theory or technique "can (and has been) tested," (2) "whether the theory or technique has been subjected to peer review and publication," (3) "the known or potential rate of error" of the technique, and (4) whether the methodology has attained general acceptance in the scientific community. *Daubert*, 509 U.S. at 593-94. The district court concluded that with the exception of the first factor--whether the theory can and has been tested (which the court assumed to be satisfied)--the *Daubert* factors favored the exclusion of Dr. Healy's testimony. *Miller v. Pfizer*, 196 F. Supp. 2d 1062, 1072-85 (D. Kan. 2002). Because of the thoroughness of the district court's published opinion, our summary of its ruling is brief.

In analyzing the peer-review-and-publication factor, the court concluded that although Dr. Healy had published peer-reviewed [**11] articles expressing the theory that Zoloft causes suicide, his specific calculations of the risk of suicide had not been subjected to peer review. *Id.* at 1073 & n.32. With regard to the rate-of-error factor, the court noted several problems with Dr. Healy's healthy- volunteer study that were identified by the independent experts: (1) the study did not

include a placebo control, (2) it involved extensive interaction between the participants and researchers, and (3) it utilized only a small sample size. *Id.* at 1074. The court accordingly concluded that the study did not include controls sufficient to demonstrate that Zoloft causes suicide in some patients. *Id.* at 1075.

Addressing the fourth *Daubert* factor, the court found that Dr. Healy had not utilized a generally accepted methodology in forming his opinions. Again referring to flaws in the design of the healthy-volunteer study, the court determined that reliance on the study did not constitute a generally accepted methodology for assessing any causal relationship between Zoloft and suicide. *Id.* at 1076. The court [*1331] also decided that placing substantial emphasis [**12] on a few challenge-dechallenge-rechallenge studies and case reports is not a generally accepted methodology. *Id.* Because the court-appointed experts could not confirm the calculations Dr. Healy made through his meta-analysis of Pfizer's data, the court likewise ruled that his use of the meta-analysis was not a generally accepted methodology. *Id.* at 1078. Finally, the court decided that Dr. Healy's purported application of Koch's postulates was not a generally accepted methodology. The court concluded that Dr. Healy "misapplied, failed to satisfy, or failed to address six of the seven postulates . . . [; and] to compound this problem, he has invented other factors and variously applied or misapplied them in ways which make it impossible to discern what his conclusions would be if they rested only on generally accepted methodology." *Id.* at 1084.

The district court decided to exclude Dr. Healy's testimony on general causation (whether Zoloft can cause suicide). It described his theory as being a "distinctly minority position" resting on only "a handful of case reports," and it characterized the "flaws in Dr. Healy's methodology" as "glaring, overwhelming [**13] and unexplained." *Id.* at 1085.

The district court also excluded Dr. Healy's testimony on the issue of specific causation (whether Zoloft caused Matthew Miller to commit suicide). Dr. Healy had proposed to testify "that in his opinion, based on a review of notes by Matthew, reports by Matthew's father, and the deposition of Matthew's

psychiatrist, Zoloft more likely than not caused Matthew to commit suicide and no other factor in his background or psychosocial situation could explain his suicide." *Id.* at 1085. Concerned, however, about "Dr. Healy's reliance on pre-selected evidence from interested parties, to the exclusion of reliable evidence that Matthew engaged in suicidal thoughts and behavior before he first used Zoloft," the court had "asked its independent experts whether selective reliance was consistent with generally accepted methodology on the issue." *Id.* at 1086. The independent experts informed the court that such selective reliance was not a generally accepted methodology. The court then concluded that "Dr. Healy's testimony on specific causation does not satisfy Rule 702 because it does not utilize sufficient facts and [**14] data and it is not the product of reliable principles and methods." *Id.* at 1087. In addition, the court noted that since it had sustained Pfizer's motion to exclude the testimony on general causation, "the issue of specific causation is for all practical purposes moot." *Id.*

Concluding that the Millers could not establish causation, the district court granted summary judgment to Pfizer.

II. DISCUSSION

On appeal the Millers contend that the district court (1) abused its discretion in restricting the information made available to the independent experts, (2) exceeded the bounds of a proper *Daubert* analysis when it excluded Dr. Healy's testimony, and (3) erred in granting summary judgment to Pfizer.

A. Information Provided to the Independent Experts

The Millers assert that they "attempted to complete the scientific record for the independent experts" by filing a consolidated statement of facts and by having Dr. Healy address the independent experts' concerns (in part by presenting at the *Daubert* hearing various power-point slides depicting graphs and calculations), but were denied that opportunity when the district court ruled that only certain information [**15] could be provided to the experts. [*1332] Aplt. Br. at 28. According to the Millers, "'freezing' Dr. Healy's opinions for nearly two years

and refusing to allow him to address concerns raised by Daubert motions filed, and independent experts appointed, after he had submitted his report (i.e., requiring their expert to answer questions in his report that had not yet been asked) constitutes an abuse of discretion." Aplt. Reply Br. at 1, & n.2. In their view, the district court erred in applying Federal Rule of Civil Procedure 26 so as to require Dr. Healy to anticipate all issues that might be raised during the course of the proceedings. They conclude that "Pfizer did not win this case in the court below on the science. They won it by a clever application of a Rule 26 'gotcha.' They won it by persuading the district court that the rules of civil procedure somehow require an expert like Dr. Healy to be prophetic." Aplt. Br. at 43.

Under Federal Rule of Civil Procedure 26(a)(2), [HN2] "a party shall disclose to other parties the identity of any person who may be used at trial to present . . . [expert testimony, and [**16] the disclosure must] be accompanied by a written report prepared and signed by the witness[,] . . . containing a complete statement of all opinions to be expressed and the basis and reasons therefor." Fed. R. Civ. P. 26(a)(2). [HN3] Supplemental disclosures are permitted, and indeed may be required. Fed. R. Civ. P. 26(e). Such supplements are to be disclosed by the time pretrial disclosures are due under Rule 26(a)(3). *See* Fed. R. Civ. P. 26(e). Failure to make proper disclosures may require exclusion of the expert as a witness. Fed. R. Civ. P. 37(c)(1). [HN4] ("A party that without substantial justification fails to disclose information required by Rule 26(a) or 26(e)(1) . . . is not, unless such failure is harmless, permitted to use as evidence at a trial, at a hearing, or on a motion any witness or information not so disclosed.")

We agree with the Millers that an expert's initial Rule 26 report cannot always anticipate every possible challenge to the report. Accordingly, on occasion it may be appropriate to permit the party [**17] using the expert to submit supplements to the report in response to assertions by opposing experts that there are gaps in the expert's chain of reasoning. [HN5] A court's failure to permit such supplementation could even constitute an abuse of discretion in some circumstances. *See Dodge v. Cotter Corp.*, 328 F.3d 1212, 1228 (10th Cir. 2003) (district courts may

abuse their discretion when deciding whether to admit expert testimony "by unreasonably limiting the evidence upon which to base the decision"). Where we depart from the Millers is that we find no abuse of discretion here.

To begin with, we disagree with the Millers' assertion that the district court improperly froze Dr. Healy's opinions for nearly two years. On the contrary, the Millers were given multiple opportunities to revise the opinions expressed in Dr. Healy's first Rule 26 report of August 13, 1999. The Millers provided Pfizer with a second Rule 26 statement dated December 10, 1999 (which was filed on April 18, 2000, as an exhibit to Pfizer's pretrial motions), and a letter by Dr. Healy dated March 6, 2000 (filed April 28, 2000, as an exhibit to Pfizer's motion in limine No. 9). On March 27-28, 2000, Dr. [**18] Healy was deposed for ten hours. And in April 2000 the Millers presented a supplemental response, and then a second supplemental response, to Pfizer's requests for admission. Both responses contained opinions of Dr. Healy.

Of particular significance are the submissions that respond to critiques of Dr. Healy's opinions. In April 2000 Pfizer filed a motion to exclude Dr. Healy's testimony. The motion alleged numerous gaps [*1333] in Dr. Healy's testimony. For example, Pfizer asserted that Dr. Healy had "no data showing any higher rate of suicide in Zoloft (sertraline) patients than in unmedicated (placebo) patients," and it criticized Dr. Healy for not conducting a statistical analysis of available data. Aplt. App. at 254, 256. Pfizer also challenged Dr. Healy's application of Koch's postulates in some detail, with its basic argument being that he "grossly misapplied six of Koch's seven postulates and . . . failed to apply, or even mention, the seventh at all." *Id.* at 264. In addition, Pfizer contended that case reports "are not a reliable basis for an expert to opine on general causation." *Id.* at 273. The Millers had an opportunity to respond to Pfizer's motion; and their response [**19] (filed May 12, 2000) included a declaration by Dr. Healy dated May 9, 2000.

Then, in August 2000 the district court issued its order to show cause why it should not appoint independent experts. In the order the court expressed concern regarding Dr. Healy's

application of Koch's postulates. It also raised questions about Dr. Healy's healthy-volunteer study, noting that the parties disagreed as to whether a placebo control is necessary and as to whether the study could form the basis for a calculation of statistically significant relative risk. The Millers had an opportunity to respond to this order; and their supplemental response (submitted on September 11, 2000), included a declaration of Dr. Healy (dated August 31, 2000) addressing the concerns expressed in the court's order.

Up to that time the district court had not rejected any submissions in support of Dr. Healy's opinions. The independent experts were provided all these submissions, including the declaration specifically addressing concerns expressed in the court's show-cause order.

The Millers' grievance relates to restrictions on their responses to the report of the independent experts, issued on September 4, 2001. In [**20] general, the report expresses unfavorable opinions regarding Dr. Healy's analysis and theories. The independent experts shared the concern expressed in the court's show-cause order that parts of Dr. Healy's approach to evaluating causation were not consistent with Koch's postulates, citing for example: "a) applying some of the postulates solely to the association of sertraline and akathisia, or to the association of sertraline and improvement in symptoms of depression, rather than maintaining a focus on the association of sertraline and suicide, and b) discounting the possibility of sertraline reducing the incidence of suicide that would be observed without treatment." Aplt. App. at 367. They also determined that Dr. Healy's "methodology for determining medical causation has not been accepted in the relevant scientific community," and concluded that his heavy reliance on case reports was not a generally accepted methodology for assessing strength of association *Id.* at 370. Moreover, they "[found] the premise that [randomized controlled trials] are undesirable for evaluating a potential sertraline-suicide association to be flawed." *Id.* at 371 (internal citation omitted). [**21] Similarly flawed, in their opinion, was Dr. Healy's comment that suicide is "vanishingly low" among 13-year-olds. *Id.* at 371-72 They also expressed concern about Dr. Healy's failure to rule out alternative

explanations, and they stated that they were unable to replicate Dr. Healy's calculation of the relative risk of suicidal acts by persons on Zoloft compared to placebo. In addition, they concluded that Dr. Healy's healthy-volunteer study did not produce statistically significant results.

In October 2001, responding to the experts' report, the Millers attempted to file their Consolidated Statement of Facts. [*1334] The district court refused to provide the independent experts with the statement.

The district court held the *Daubert* hearing on November 19-20, 2001. Dr. Healy was afforded an opportunity to respond to the concerns the court articulated in its show-cause order. He was, for example, permitted to explain his relative-risk calculation. At the hearing the parties' attorneys questioned Dr. Healy and the independent experts, and the independent experts in turn were permitted to question Dr. Healy. The district court did, however, preclude Dr. Healy from discussing information [**22] that had not previously been provided to the independent experts. It also refused to let Dr. Healy give a power-point presentation depicting various graphs and calculations.

The Millers now argue that the district court abused its discretion in refusing to make their Consolidated Statement of Facts available to the court-appointed experts and in limiting the information that the independent experts could consider at the *Daubert* hearing. They assert that "they repeatedly implored the court to permit them and their expert witness to provide the independent expert with ALL of the scientific information currently available both from the public domain and from Pfizer internal documents, to answer any questions and concerns that the experts might have." Aplt. Br. at 6. They further say that they "urged that Dr. Healy be permitted to provide data and analysis from all of the information to which he had . . . been privy, including Pfizer's own healthy volunteer studies, which he reviewed in November 1999." *Id.* at 7. The Millers, however, have failed to establish an abuse of discretion.

Well before issuance of the independent experts' report, the Millers had been alerted to a number [**23] of concerns

regarding Dr. Healy's opinions, and they had been afforded ample opportunity to submit Dr. Healy's responses to those concerns. The independent experts' embrace of many of these concerns did not require the court to grant Dr. Healy a further opportunity to persuade the court (and the independent experts) by offering new data, analyses, and theories that could have been included in prior submissions. [HN6] The orderly conduct of litigation demands that expert opinions reach closure. *Cf. Daubert*, 509 U.S. at 597 ("Scientific conclusions are subject to perpetual revision. Law, on the other hand, must resolve disputes finally and quickly.").

The Millers have failed to point to anything they proffered that was responsive only to matters in the independent experts' report that had not been raised previously by Pfizer or the district court. In particular, the Millers have provided no explanation how the assertedly crucial information contained in their Consolidated Statement of Facts was responsive to concerns raised for the first time by the independent experts. They likewise have not demonstrated why they could not have presented this information before the independent [**24] experts submitted their report. Nor do the Millers explain why it was unfair of the district court to refuse to permit Dr. Healy to make the power-point presentation that he attempted to give at the *Daubert* hearing. The power-point slides were based on data that the Millers acquired before Dr. Healy's expert report was due. The Millers offer no reasons why Dr. Healy could not have produced his analysis long before. The day of the hearing was a bit late to try to buttress the theory of their case by producing a new analysis by their retained expert of long-available data.

Our decision today is not based on a rigid application of the rules of civil procedure. [HN7] *See* Fed. R. Civ. P. 1 ("These rules . . . shall be construed and administered to secure the just, speedy, and inexpensive [*1335] determination of every action."). Far from improperly freezing Dr. Healy's opinions or holding him to his first Rule 26 statement, the district court allowed Dr. Healy to express revised opinions on numerous occasions. The district court exhibited patience and concern for fairness to both sides. It did not abuse its discretion.

B. Exclusion of Dr. Healy's [25] Testimony**

[HN8] "We review de novo the question of whether the district court performed its gatekeeper role and applied the proper legal standard in admitting an expert's testimony. We then review for abuse of discretion the trial court's actual application of the gatekeeper standard in deciding whether to admit or exclude an expert's testimony." *Goebel v. Denver & Rio Grande W. R.R. Co.*, 346 F.3d 987, 989-90 (10th Cir. 2003) (internal citations omitted).

The Millers' focus is on the first type of review, whether the district court exceeded the scope of a proper *Daubert* inquiry. In their view, the district court followed *Daubert* "for a while," but then "**went beyond** . . . [*Daubert*] . . . to nit-pick bits and pieces of Dr. Healy's work and to question whether or not those portions followed proper scientific methodology." Aplt. Br. at 30. The court erred, they argue, "by straying far beyond the proper scope of the *Daubert* . . . matrix of analysis, and premising an exclusionary decision on concerns or questions which affect the weight rather than the admissibility of Dr. Healy's testimony." *Id.* at 42. We disagree.

The district [**26] court carefully followed *Daubert* in determining whether Dr. Healy's opinions were founded on scientific principles. What the Millers call nit-picking, we would call being thorough. [HN9] "The analysis outlined in *Daubert* is extensive, requiring the district court to carefully and meticulously review the proffered scientific evidence." *United States v. Call*, 129 F.3d 1402, 1405 (10th Cir. 1997) (internal quotation marks omitted). The court did not exceed the scope of the *Daubert* inquiry by, for example, considering Dr. Healy's credibility or weighing the evidence. *See McCullock v. H.B. Fuller Co.*, 61 F.3d 1038, 1045 (2d Cir. 1995); *Ambrosini v. Labarraque*, 322 U.S. App. D.C. 19, 101 F.3d 129, 141 (D.C. Cir. 1996). Rather, substantially relying on the opinions of the court-appointed experts, the court carefully and properly performed its gatekeeping function under *Daubert*.

Furthermore, to the extent that the Millers argue that the district court abused its discretion in applying the gatekeeper

standard, we find no abuse of discretion. We hold that the district court did not err in excluding Dr. Healy's testimony.

C. The [**27] Court's Decision to Grant Summary Judgment

Following the exclusion of Dr. Healy's testimony, the district court ruled that the Millers' claim must be dismissed as a matter of law because they had "no scientific evidence of general causation." *Miller v. Pfizer*, 196 F. Supp. 2d at 1125. The Millers contended at oral argument before us, however, that they had enough evidence to avoid summary judgment even without Dr. Healy's testimony because Pfizer made an admission that, in and of itself, establishes general causation. [HN10] We need not address this argument because it was not raised in their appellate briefs. *See Federal Ins. Co. v. Tri-State Ins. Co.*, 157 F.3d 800, 805 (10th Cir. 1998). Nor have the Millers shown that they made this argument in district court. The district court's opinion states that "to support their claim of general causation, plaintiffs have relied *exclusively* on the testimony of Dr. Healy." *Miller*, 196 F. Supp. 2d at 1125 ([*1336] emphasis added). [HN11] We need not consider an argument made for the first time on appeal. *See Smith v. Rogers Galvanizing Co.*, 128 F.3d 1380, 1385-86 (10th Cir. 1997).

[**28] III. CONCLUSION

We AFFIRM the summary judgment below. In addition, we grant Pfizer's Motion to Strike (filed December 16, 2002), and deny Pfizer's Motion to Take Judicial Notice (filed December 16, 2002), the Millers' Request for Judicial Notice (filed November 3, 2003), and the Millers' Second Request for Judicial Notice (filed December 19, 2003).

UNITED STATES DISTRICT COURT

DISTRICT OF KANSAS

JUDGMENT IN A CIVIL CASE

MARK MILLER and CHERYL MILLER, individually and MARK MILLER, as Administrator of the Estate of Matthew Miller, Deceased,

Plaintiffs,

v.

CIVIL NO. 99-2326-KHV

PFIZER INC. (Roerig Division),

Defendant.

( ) **JURY VERDICT.** This action came before the Court for a trial by jury. The issues have been tried and the jury has rendered its verdict.

(X) **DECISION BY THE COURT.** This action came to decision by the Court. The issues have been considered and a decision has been rendered.

IT IS ORDERED AND ADJUDGED that pursuant to the Memorandum and Order filed February 11, 2002, Defendant Pfizer Inc's Motion For Partial Summary Judgment On Plaintiffs' Claim Of Marketing Defect And Misrepresentation (Doc. #505) is SUSTAINED.

IT IS FURTHER ORDERED AND ADJUDGED that pursuant to the Memorandum and Order filed February 11, 2002, Defendant Pfizer Inc's Motion For Partial Summary Judgment On Plaintiffs' Failure To Warn Claim (Doc. #504) is SUSTAINED.

IT IS FURTHER ORDERED AND ADJUDGED that plaintiffs take nothing and the action is dismissed on the merits.

Dated: February 11, 2002

RALPH L. DeLOACH, CLERK

Linda South

Linda South, Deputy Clerk

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FDA Public Health Advisory

March 22, 2004

Subject: WORSENING DEPRESSION AND SUICIDALITY IN PATIENTS BEING TREATED WITH ANTIDEPRESSANT MEDICATIONS

Today the Food and Drug Administration (FDA) asked manufacturers of the following antidepressant drugs to include in their labeling a Warning statement that recommends close observation of adult and pediatric patients treated with these agents for worsening depression or the emergence of suicidality. The drugs that are the focus of this new Warning are: Prozac (fluoxetine); Zoloft (sertraline); Paxil (paroxetine); Luvox (fluvoxamine); Celexa (citalopram); Lexapro (escitalopram); Wellbutrin (bupropion); Effexor (venlafaxine); Serzone (nefazodone); and Remeron (mirtazapine).

Warning Information

- Health care providers should carefully monitor patients receiving antidepressants for possible worsening of depression or suicidality, especially at the beginning of therapy or when the dose either increases or decreases. Although FDA has not concluded that these drugs cause worsening depression or suicidality, health care providers should be aware that worsening of symptoms could be due to the underlying disease or might be a result of drug therapy.

- Heath care providers should carefully evaluate patients in whom depression persistently worsens, or emergent suicidality is severe, abrupt in onset, or was not part of the presenting symptoms, to determine what

intervention, including discontinuing or modifying the current drug therapy, is indicated.

- Anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia (severe restlessness), hypomania, and mania have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although FDA has not concluded that these symptoms are a precursor to either worsening of depression or the emergence of suicidal impulses, there is concern that patients who experience one or more of these symptoms may be at increased risk for worsening depression or suicidality. Therefore, therapy should be evaluated, and medications may need to be discontinued, when symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

- If a decision is made to discontinue treatment, certain of these medications should be tapered rather than stopped abruptly (see labeling for individual drug products for details).

- Because antidepressants are believed to have the potential for inducing manic episodes in patients with bipolar disorder, there is a concern about using antidepressants alone in this population. Therefore, patients should be adequately screened to determine if they are at risk for bipolar disorder before initiating antidepressant treatment so that they can be appropriately monitored during treatment. Such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

- Health care providers should instruct patients, their families and their caregivers to be alert for the emergence of agitation, irritability, and the other symptoms described above, as well as the emergence of suicidality and worsening depression, and to report such symptoms immediately to their health care provider.

Background

Among antidepressants, only Prozac (fluoxetine) is approved for the treatment of pediatric major depressive disorder. Prozac (fluoxetine), Zoloft (sertraline), and Luvox (fluvoxamine) are approved for pediatric obsessive compulsive disorder. None of these drugs is approved as monotherapy for use in treating bipolar depression, either in adults or children.

The requested labeling changes are consistent with recommendations made to the Agency at a meeting of the Psychopharmacological Drugs Advisory Committee (PDAC) and the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee (Peds AC), held on February 2, 2004. The possibility of suicidality associated with the use of antidepressant drug products in the pediatric population was also the subject of two previous FDA communications (FDA Talk Paper on June 19, 2003, and FDA Public Health Advisory on October 27, 2003).

FDA is continuing to review available clinical trial data for pediatric patients with depression and other psychiatric disorders to try to determine whether there is evidence that some or all antidepressants increase the risk of suicidality. Later this summer, the FDA plans to update the PDAC and Peds AC about the results of this review.

FDA plans to work closely with each of the nine manufacturers of the antidepressants that are the subject of today's request to continue investigating how to optimize the safe use of these drugs and implement the proposed labeling changes and other safety communications in a timely manner.

Date created: March 22, 2004

FDA Talk Paper

1. T04-08
March 22, 2004

Media Inquiries: 301-827-6242
Consumer Inquiries: 888-INFO-FDA

FDA Issues Public Health Advisory on Cautions for Use of Antidepressants in Adults and Children

The Food and Drug Administration today issued a Public Health Advisory that provides further cautions to physicians, their patients, and families and caregivers of patients about the need to closely monitor both adults and children with depression, especially at the beginning of treatment, or when the doses are changed with either an increase or decrease in the dose.

FDA has been closely reviewing the results of antidepressant studies in children, since June 2003, after an initial report on studies with paroxetine (Paxil), and subsequent reports on studies of other drugs, appeared to suggest an increased risk of suicidal thoughts and actions in the children given antidepressants. There were no suicides in any of the trials. On close examination of the initial reports, it was unclear whether certain behaviors reported in these studies represented actual suicide attempts, or other self-injurious behavior that was not suicide-related.

FDA has initiated a full review of these reported behaviors by experts in such evaluation. However, it is not yet clear whether antidepressants contribute to the emergence of suicidal thinking and behavior. The agency is advising clinicians, patients, families and caregivers of adults and children that they should closely monitor all patients being placed on therapy with these drugs for worsening depression and suicidal thinking, which can

occur during the early period of treatment. The agency is also advising that these patients be observed for certain behaviors that are known to be associated with these drugs, such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia (severe restlessness), hypomania, and mania, and that physicians be particularly vigilant in patients who may have bipolar disorder.

FDA is asking manufacturers to change the labels of ten drugs to include stronger cautions and warnings about the need to monitor patients for the worsening of depression and the emergence of suicidal ideation, regardless of the cause of such worsening.

The drugs under review include bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, escitalopram and venlafaxine. It should be noted that the only drug that has received approval for use in children with major depressive disorder is fluoxetine (Prozac). Several of these drugs are approved for the treatment of obsessive-compulsive disorder in pediatric patients, i.e., sertraline (Zoloft), fluoxetine (Prozac), and fluvoxamine (Luvox). Luvox is not approved as an antidepressant in the United States.

These interim actions follow recommendations made by FDA's Psychopharmacologic Drugs and Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committees, which met on February 2, 2004. The advisory committee members advised FDA that the labeling should draw more attention to the need to monitor patients being treated with certain antidepressants.

FDA has previously noted (in Public Health Advisory and a Talk Paper T03-70 published Oct. 27, 2003) the possible finding of increased suicidal thinking or behavior, but emphasized that it was not clear that the drugs caused such events and additional

analyses were being done to allow FDA to seek more definitive answers.

The Public Health Advisory containing the new labcl warnings and cautions is available online at http://www.fda.gov/cder/drug/antidepressants/default.htm.

Later this summer, FDA plans to update the Advisory Committees on the results of the expert analyses and its own analyses of the pediatric suicidality data.

Barton, Greenwood Seek Info
From FDA On Antidepressants

March 24, 2004

The Honorable Mark B. McClellan, M.D., Ph.D.
Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Commissioner McClellan:

As part of its continuing oversight of the public health and the safety of prescription drugs, the Committee is examining issues surrounding the safety and efficacy of anti-depressants in the pediatric/adolescent population. We understand that the Food and Drug Administration ("FDA") has had a longstanding concern about the possibility of increased risk of suicidality in the adult population taking anti-depressants, specifically Prozac, and convened an advisory committee meeting in 1991 to discuss this matter. At that time, the FDA concluded that the available data did not appear to support a finding that Prozac caused an increased risk of suicide in adults and did not require any labeling changes on the products. We also understand that over the next 12 years, the FDA continued to monitor and study this issue amid conflicting scientific reports, some suggesting there may be an increased risk for suicidal behavior from the use of anti-depressants. Further, during this time period, several companies were conducting clinical trials of their anti-depressants, approved by the FDA to treat adults, in the pediatric population with the goal of gaining FDA approval for use in children.

Two important factual questions of interest to the Committee are the following: (1) What did the FDA know about issues of safety and efficacy of anti-depressants in children after these companies submitted their data from these clinical trials? and (2) When was the FDA provided a complete set of pediatric clinical data from the respective companies. The answer to these questions will assist the Committee in assessing: the risks and benefits of anti-depressants used in children; whether the FDA informed the public in a timely and thorough manner about the risks for the pediatric population; whether the FDA adequately evaluated the data relating to both the efficacy and potential risks of suicide in children taking anti-depressants; and whether additional legislative or regulatory action will be, or should be, taken with respect to the labeling of these products.

According to a January 5, 2004 written memorandum by Dr. Thomas Laughren of the FDA, 12 of 15 studies involving children with major depressive disorder ("MDD"), that were done in accordance with the FDA's written protocol, showed no efficacy when comparing the drug to a placebo. Dr. Laughren stated, "[t]he overall success rate for positive studies of 20% (3/15) is clearly a concern." We note that, in addition to the seeming lack of demonstrated efficacy in this data set, Dr. Laughren in his comments also indicated a potential signal for increased risk in suicide attempts and/or suicide-related behavior in five out of seven anti-depressants tested in pediatric clinical trials.

We note that while there were issues of safety and efficacy before the FDA, the off-label prescription of anti-depressants for children with MDD is significant. To date, we understand that the FDA has approved only Prozac for use in children with MDD. In addition, Prozac, Zoloft and Luvox also have been approved by the FDA for use in children diagnosed with Obsessive Compulsive Disorder ("ODC"). Despite the limited

number of FDA approved anti-depressants for use in children, and the narrow class of disorders for which they have been approved, prescriptions for anti-depressants in children continues to be on the rise. According to data presented by the FDA at the February 2, 2004 Advisory Committee meeting, in 2002, there were over 10 million anti-depressant prescriptions for children ages 1-17 years of age in the United States. Of these 10 million prescriptions, approximately 2.2 million (20%) were written for Paxil, an anti-depressant with no approval for any indication in children. According to the FDA, Paxil was the second most prescribed anti-depressant in the United States pediatric population in 2002, despite the lack of any FDA approval for use in children.

Given the widespread use of Paxil in the U.S. pediatric/adolescent population, on June 19, 2003, the FDA issued an advisory concerning the use of Paxil in adolescents and children with MDD due to possible increased risks of suicide-related behavior. It is our understanding that the FDA's action was based on newly analyzed pediatric data that had been recently provided by GlaxoSmithKline, the manufacturer of Paxil, to the FDA and other foreign medical regulatory authorities, indicating there appears to be a signal for suicide-related behavior in children and adolescents using Paxil. The FDA followed up this product-specific advisory warning with another general warning about the use of anti-depressants in children and adolescents on October 27, 2003.

On March 22, 2004, the FDA issued a public health advisory on the use of anti-depressants in adults and children cautioning that there should be close monitoring of potentially suicide-related behavior particularly during the beginning of treatment or when a dosage change in made. In this most recent advisory, the FDA also requested that the manufacturers of ten anti-depressants include a stronger cautionary warning about the emergence of

suicide ideation in all individuals taking anti-depressants. We do not know whether the manufacturers are required to comply with the FDA's "request" for a labeling change, and if they do, whether FDA has set up a time frame in which this labeling change must be made. To date, the FDA has not contraindicated any anti-depressants for use in children and adolescents, nor has the FDA required or requested an additional warning on the products' labels that concern the suicide-related risks that may be heightened in the pediatric population exclusively.

In contrast to the FDA's actions on this issue, the British government's medical regulatory authorities contraindicated all anti-depressants, except Prozac, for use in children and adolescents. Further, both Canada and Britain have required additional labeling on anti-depressants, such as Paxil, warning of the potential suicide-related behavioral risks in the pediatric population associated with use of the products. It is our understanding that the FDA and the British government's medical regulatory authority were provided the same data analysis from GlaxoSmithKline concerning the increased risk in suicide-related behavior in children taking Paxil. It is unclear, at this point, whether the British authorities and the FDA have the same pediatric data sets from all of the various companies marketing anti-depressants. Given the serious implications that certain anti-depressants may have for children, the Committee is interested in learning the rationale for FDA's decision not to require stronger warnings on the labeling for pediatric use of an anti-depressant product when, for example, a company's own analysis of their data indicates an increased risk of suicide-related behavior in children.

Finally, it is our understanding that beginning in the summer of 2003, and prompted by GlaxoSmithKline's disclosure of their "new" Paxil pediatric analysis, the FDA requested that the other companies that performed pediatric clinical trials on anti-

depressants re-analyze their data concerning suicide-related behavior and provide these data sets to the FDA so that the FDA may undertake a more comprehensive review of the data. According to testimony given at the February 2, 2004 Advisory Committee meeting, after several follow-up requests from FDA to the various companies, the FDA was able to get the specific types of data sets and patient level data they requested and undertook an analysis of the data. The Committee is interested in learning who at FDA undertook this analysis and the results thereof, because at this February 2, 2004 meeting, the FDA indicated they had requested a second analysis of the data by Columbia University researchers. The Columbia University analysis is expected to be completed by this summer.

A recent press report raises a question about whether an FDA official, tasked with evaluating the pediatric clinical trial data relating to potential suicidal risks, was prevented from presenting a report with his conclusions at the February 2 Advisory Committee meeting. On February 1, 2004 the San Francisco Chronicle reported that Andrew Mosholder, an FDA Medical Officer, was "barred from publicly presenting his finding that several leading antidepressants may increase the risk of suicidal behaviors among children." The article states that Dr. Mosholder, with the FDA's Office of Drug Safety, was charged with reviewing data from 20 clinical trials involving over 4,100 children. An anonymous FDA official was quoted as stating that Dr. Mosholder was told by Russell Katz, director of FDA's Division of Neuropharmacological Drug Products, that he would not be able to present his report because he had reached a conclusion and, therefore, was biased. Another FDA official, Anne Trontell, indicated that Dr. Mosholder's analysis would not be presented at the February 2 meeting because it was not a finalized document. We note that the transcript of the February 2 meeting reflects that Dr. Mosholder did not present a report on

his evaluation of the anti-depressant pediatric clinical trial data concerning suicide-related behavior.

The Committee is interested in learning what Dr. Mosholder's role was in the review of the pediatric clinical trial data for anti-depressants, whether Dr. Mosholder was prevented from presenting his findings a month prior to the scheduled meeting (and if so, why), and whether FDA institutional processes prevented Dr. Mosholder's report from being finalized in time for the February 2 Advisory Committee meeting (and if so, why). Further, given that the Advisory Committee agreed with FDA's recommendation that Columbia University reanalyze the pediatric anti-depressant data, the Committee is interested in learning who at FDA was knowledgeable about Dr. Mosholder's conclusions and whether his conclusions were a factor in the decision to involve an outside group, such as Columbia University, in conducting another data analysis before the FDA decides whether to take further regulatory action in this matter.

In light of the Committee's concern over the public health of children and/or the need to expedite public and physician confidence in the use of anti-depressants for children, the Committee seeks written analyses, data, correspondence and background information of clinical trials involving depressed children. To assist this investigation, we are requesting that, pursuant to Rules X and XI of the U.S. House of Representatives, you provide the Committee with the information requested below by Monday, April 5, 2004:

1. All records provided by or to the FDA in connection with the February 2, 2004 FDA Advisory Committee meeting involving the Psychopharmacological Drugs Advisory Committee (PDAC) and the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee (Peds AC), including, but not limited to,

records relating to the planning of this meeting and its agenda.

2. All records of Dr. Andrew Mosholder, Dr. Mary Willy, Dr. Russell Katz, Ms. Anne Trontell and Dr. Thomas Laughren, relating to efficacy and safety of anti-depressants in the pediatric and/or adolescent population, including, but not limited to, all draft or final reports, internal correspondence, e-mails and notes concerning pediatric or adolescent anti-depressant clinical trials and any records relating to spontaneous reports (AERS system) on the same issue.

3. All records of communication relating to anti-depressants and suicide-related risks or efficacy in the pediatric and/or adolescent population between the FDA and the following companies:

   a. Eli Lilly & Co.;
   b. Pfizer Inc.;
   c. Wyeth Pharmaceuticals;
   d. GlaxoSmithKline;
   e. Bristol-Myers Squibb Co.;
   f. Akzo Nobel Inc.; and
   g. Forest Laboratories, Inc.

4. All records relating to GlaxoSmithKline's submission of data analyses in pediatric/adolescent clinical trials involving Paxil, including, but not limited to, all submissions contained as attachments to their May 22, 2003 letter to the FDA.

5. All records relating to FDA's decision to issue the June 19, 2003 advisory on Paxil and possible effects in the pediatric/adolescent population.

6. All records relating to the FDA's decision to issue the October 27, 2003 advisory on possible effects of anti-depressants in the pediatric/adolescent population.

7. All records relating to the FDA's decision to issue the March 22, 2004 advisory on monitoring adults and children taking anti-depressants for suicidal-ideation and to request a labeling change for ten anti-depressants.
8. All records relating to communications by FDA employees that raise questions or concerns about the safety or efficacy of anti-depressants in the pediatric/adolescent population.
9. All records relating to communications that raise questions or concerns about the safety or efficacy of anti-depressants in the pediatric/adolescent population between FDA and any of the following:

    a. Eli Lilly & Co.;
    b. Pfizer Inc.;
    c. Wyeth Pharmaceuticals
    d. GlaxoSmithKline;
    e. Bristol-Myers Squibb Co.;
    f. Akzo Nobel Inc.;
    g. Forest Laboratories, Inc
    h. United Kingdom's Medicines and Healthcare Products Regulatory Agency; or
    i. A U.S. state or federal governmental agency.

10. All records relating to communications concerning proposed or finalized labeling changes with respect to warnings about the safety or efficacy of anti-depressants in the pediatric/adolescent population including, but not limited to, Wyeth's independent decision to change the labeling on Effexor with respect to safety risks in children.
11. A listing of all the pediatric/adolescent clinical trials involving anti-depressants that the FDA received data for which there was an obligation for the company to submit

the data to the FDA. For each such trial, include the following information:

a. Name of the company;
b. Name of the anti-depressant;
c. Date when pediatric clinical trial data was submitted to FDA;
d. Date when pediatric clinical trial was completed by company;
e. Summary of FDA's "response" to the clinical trial and what, if any, regulatory action FDA took with respect to approving the particular drug for an indication in the pediatric population.

12. State the person(s) at FDA responsible for evaluating and providing a written analysis of the data that was requested by FDA, in the summer and fall of 2003, from various manufacturers of anti-depressants who performed clinical trials in children.

Please note that, for purposes of responding to this request, the terms "records" and "relating" should be interpreted in accordance with the attachment to this letter. In addition to the above requested materials, the Committee staff would also like to set up a mutually convenient time to interview: Andrew Mosholder, Thomas Laughren, Russell Katz, Ann Trontell, Mary Willy, Paul Seligman, Syed Ahmad, Katherine Gelperin, Rita Quellett-Hellstrom, Caroline McCloskey, Parivash Nourjah, Alan Brinker, Mark Avigan, Diane Wysowski, David Graham, Judy Staffa, Cindy Kornegay, and Lois LaGrenade.

In order to set up the requested interviews, as well to answer any questions you may have on this matter, please contact Alan Slobodin at (202) 225-2927 or Kelli Andrews at (202) 226-2424 of the Committee Staff.

Sincerely,

Joe Barton
Chairman

James C. Greenwood
Chairman

Subcommittee on Oversight and Investigations

cc: The Honorable John D. Dingell, Ranking Member
The Honorable Peter Deutsch, Ranking Member
Subcommittee on Oversight and Investigations

Attachment

1. The term "records" is to be construed in the broadest sense and shall mean any written or graphic material, however produced or reproduced, of any kind or description, consisting of the original and any non-identical copy (whether different from the original because of notes made on or attached to such copy or otherwise) and drafts and both sides thereof, whether printed or recorded electronically or magnetically or stored in any type of data bank, including, but not limited to, the following: correspondence, memoranda, records, summaries of personal conversations or interviews, minutes or records of meetings or conferences, opinions or reports of consultants, projections, statistical statements, drafts, contracts, agreements, purchase orders, invoices, confirmations, telegraphs, telexes, agendas, books, notes, pamphlets, periodicals, reports, studies, evaluations, opinions, logs, diaries, desk calendars, appointment books, tape recordings, video recordings, e-mails, voice mails, computer tapes, or other computer stored matter, magnetic tapes, microfilm, microfiche, punch cards, all other records kept by electronic, photographic, or mechanical means, charts,

photographs, notebooks, drawings, plans, inter-office communications, intra-office and intra-departmental communications, transcripts, checks and canceled checks, bank statements, ledgers, books, records or statements of accounts, and papers and things similar to any of the foregoing, however denominated.

2. The terms "relating," "relate," or "regarding" as to any given subject means anything that constitutes, contains, embodies, identifies, deals with, or is in any manner whatsoever pertinent to that subject, including but not limited to records concerning the preparation of other records.

Related Documents

News Release
Energy and Commerce Leaders Questioning U.S. Oncology
June 26, 2003

Energy and Commerce Leaders Questioning U.S. Oncology
Letter to Mr. R. Dale Ross
U.S. Oncology
June 26, 2003

The Safety and Efficacy of Pharmaceuticals Imported into the United States
Letter to The Honorable Mark McClellan
Food and Drug Administration
June 5, 2003

News Release
Tauzin, Greenwood Examine FDA's Adequacy on Food Import Controls
June 11, 2003

Tauzin, Greenwood Examine FDA's Adequacy on Food Import Controls
Letter to The Honorable Mark McClellan
Food and Drug Administration
June 11, 2003

Energy and Commerce Leaders Expand Investigation of Skinny Pill for Kids
Letter to Ms. Edita Kaye
The Skinny Pill
March 25, 2003

News Release
Energy and Commerce Leaders Initiate Examination of Ephedra
February 28, 2003

More On FDA

333.99 Neuroleptic-Induced Acute Akathisia

Diagnostic Features

The essential features of Neuroleptic-Induced Acute Akathisia are subjective complaints of restlessness and at least one fo the following observed movements: fidgety movements or swinging of the legs while seated, rocking rom foot to foot or "walking on the spot" while standing, pacing to relieve the restlessness, or an inability to sit or stand still for at least several minutes. In its most severe form, the individual may be unable to maintain any position for more than a few seconds. The subjective complaints include a sense of inner restlessness, most often in the legs; a compulsion to move one's legs; distress if one is asked not to move one's legs; and dysphoria and anxiety. The symptoms typically occur within four weeks of initiating or increasing the dose of neuroleptic medication and can occasionally follow the reduction of medication used to treat or prevent acute extrapyramidal symptoms (e.g., anticholinergic agents). The symptoms are not better accounted for by a mental disorder (e.g., Schizophrenia, Substance Withdrawal, agitation from a Major Depressive or Manic Episode, hyperactivity in Attention-Deficit/Hyperactivity Disorder) and are not due to a non-neuroleptic substance or to a neurological or other general medical condition (e.g., Parkinson's disease, iron-deficiency anemia).

Associated Features and Disorders

The subjective distress resulting from akathisia is significant and can lead to noncompliance with neuroleptic treatment. Akathisia may be associated with dysphoria, irritability, aggression, or suicide attempts. Worsening of psychotic symptoms or behavioral dyscontrol may lead to an increase in neuroleptic medication does, which ma exacerbate the problem. Akathisia can develop very rapidly after initiating or increasing neuroleptic

medication. The development of akathisia appears to be dose dependent and to be more frequently associates with particular neuroleptic medications. Acute akathisia tends to persist for as long as neuroleptic medications are continued, although the intensity may fluctuate over time. The reported prevalence of akathisia among individuals receiving neuroleptic medication has varied widely (20%-75%). Although the atypical neuroleptic medications are less likely to cause akathisia than the typical neuroleptics, nonetheless, these medications do cause akathisia in some individuals. Variations in reported prevalence may be due to a lack of consistency in the definition of caseness, neuroleptic prescribing practices, study design, and the demographics of the population being studied.

Differential Diagnosis

Neuroleptic-Induced Acute Akathisia may be clinically indistinguishable from syndromes of restlessness due to certain neurological or other general medical conditions, to nonneuroleptic substances, and to agitation presenting as part of a mental disorder (e.g., a Manic Episode). The akathisia of Parkinson's disease and iron-deficiency anemia are phenomenologically similar to Neuroleptic-Induced Acute Akathisia. The frequently abrupt appearance of restlessness soon after initiation or increase in neuroleptic medication usually distinguishes Neuroleptic-Induced Acute Akathisia.

Serotonin-specific reuptake inhibitor antidepressant medications may produce akathisia that appears to be identical in phenomenology and treatment response to Neuroleptic-Induced Acute Akathisia. Akathisia due to nonneuroleptic medication can be diagnosed as Medication-Induced Movement Disorder Not Otherwise Specified. Other situations that might be included under Medication-Inducted Movements Disorder Not Otherwise Specified are acute akathisia with only subjective or

only objective complaints, but not both; and akathisia occurring late in the course of treatment (e.g., six months after initiation of, or increase in the dose of, a neuroleptic). Neuroleptic-Induced Tardive Dyskinesia also often has a component of generalized restlessness that may coexist with akathisia in an individual receiving neuroleptic medication. Neuroleptic-Induced Acute Akathisia is differentiated from Neuroleptic-Induced Tardive Dyskinesia by the nature of the movements and their relationship to the initiation of medication. The time course of symptomatic presentation relative to neuroleptic dose changes may aid in this distinction. An increase in neuroleptic medication will often exacerbate akathisia, whereas it often temporarily relieves the symptoms of Tardive Dyskinesia.

Neuroleptic-Induced Acute Akathisia should be distinguished from symptoms that are better accounted for by a mental disorder. Individuals with Depressive Episodes, Manic Episodes, Generalized Anxiety Disorder, Schizophrenia and other Psychotic Disorders, Attention-Deficit/Hyperactivity Disorder, dementia, delirium, Substance Intoxication (e.g., with cocaine), or Substance Withdrawal (e.g., from an opioid) may also display agitation that is difficult to distinguish from akathisia. Some of these individuals are able to differentiate akathisia from the anxiety, restlessness, and agitation characteristic of a mental disorder by their experience of akathisia as being different from previously experienced feelings. Other evidence that restlessness or agitation may be better accounted for by a mental disorder includes the onset of agitation prior to exposure to the neuroleptic medication, absence of increasing restlessness with increasing neuroleptic medication doses, and absence of relief with pharmacological interventions (e.g., no improvement after decreasing the neuroleptic dose or treatment with medication intended to treat the akathisia).

Research criteria for 333.99 Neuroleptic-Induced Acute Akathisia

A. The development of subjective complaints of restlessness after exposure to a neuroleptic medication.

B. At least one of the following is observed:

(1) fidgety movements or swinging of the legs
(2) rocking from foot to foot while standing
(3) pacing to relieve restlessness
(4) inability to sit or stand still for at least several minutes

C. The onset of the symptoms in Criteria A and B occurs within four weeks of initiating or increasing the dose of the neuroleptic, or of reducing medication used to treat (or prevent) acute extrapyramidal symptoms (e.g., anticholinergic agents).

D. The symptoms in Criterion A are not better accounted for by a mental disorder (e.g., Schizophrenia, Substance Withdrawal, agitation from a Major Depressive or Manic Episode, hyperactivity in Attention-Deficit/Hyperactivity Disorder). Evidence that symptoms may be better accounted fro by a mental disorder might include the following: the onset of symptoms preceding the exposure to the neuroleptics, the absence of increasing restlessness with increasing neuroleptic doses, and the absence of relief with pharmacological interventions (e.g., no improvement after decreasing the neuroleptic dose or treatment with medication intended to treat the akathisia).

E. The symptoms in Criterion A are not due to a nonneuroleptic substance or to a neurological or other general medical condition. Evidence that symptoms are due to a general medical condition might include the onset of the symptoms preceding the exposure to neuroleptics or the progression of symptoms in the absence of a change in medication.

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF KANSAS

MARK MILLER AND	§	
CHERYL MILLER	§	
INDIVIDUALLY AND	§	
MARK MILLER AS	§	
ADMINISTRATOR OF THE	§	
ESTATE OF	§	
MATTHEW MILLER,	§	
DECEASED	§	
Plaintiffs	§	NO. 99-2326 KHV
	§	
v.	§	
	§	
PFIZER, INC. (Roerig Division)	§	
Defendant	§	

ORDER TO SHOW CAUSE

This matter comes before the Court on Defendant Pfizer Inc.'s Motion to Exclude the Testimony of David Healy (Doc. #217) filed April 18, 2000. Dr. Healy opines that Zoloft general causes suicide and that it specifically caused Matthew Miller to commit suicide. Defendant argues (1) that Dr. Healy's testimony will not assist the trier of fact because he is unable to show a statistically significant relative risk; (2) that he improperly uses Koch's postulates; (3) that his testimony fails to

satisfy the standards set out in Daubert v. Merrell Dow Pharm., 509 U.S. 579 (1993); (4) that his opinions are not based on data on which others in the field would reasonably rely; and (5) that he is unqualified to offer opinions regarding warnings, regulatory matters and suicidology.

After reviewing the parties' briefs on the issue, the Court believes that an independent expert witness would be helpful in determining whether Dr. Healy's methodology is proper under Daubert. D.Kan. Rule 26.4 states in part:

> If a judge determines that the appointment of expert witnesses in an action may be desirable the judge shall order the parties to show cause why expert witnesses should not be appointed, and after opportunity for hearing, may request nominations and appoint one or more such witnesses. If the parties agree in the selection of an expert or experts, only those agreed upon shall be appointed. Otherwise, the judge may make the selection. The judge shall determine the duties of the witness and inform the witness thereof at a conference at which the parties shall have an opportunity to participate.

The Court believes that an independent expert would greatly assist its evaluation of Dr. Healy's methodology and

whether it satisfies the four factors set forth in Daubert: (1) whether the proffered technique can be and has been tested; (2) whether the technique or theory has been subject to peer review; (3) the known or potential rate of error; and (4) the general acceptance of a technique in the relevant scientific community. 509 U.S. at 593-94. The proponent of expert testimony must show "a grounding in the methods and procedures of science which must be based on actual knowledge and not subjective belief or unaccepted speculation." Mitchell v. Gencorp. Inc., 165 F.3d 778, 780 (10th Cir. 1999).

Dr. Healy's opinion is based on his application of Koch's postulates, factors that guide scientists in making judgments about causation. Federal Judicial Center, Reference Manual on Scientific Evidence (1994) at 161. While Koch's postulates are clearly a proper methodology for forming such judgments, the Court has questions regarding Dr. Healy's application of the postulates in this case.

The first postulate concerns the strength of the association between the exposure and effect. While "relative risk is one of the cornerstones for causal inferences," see Reference Manual at 161, Dr. Healy disavows the need for an epidemiological study. See Appendix of Exhibits (Nos. 86 to 99) to Defendant Pfizer Inc.'s Pretrial Motions (Doc. #232), Ex. 91 at 0000083. Instead, in finding a strong association, he relies heavily upon case reports. The Court is not convinced at this point that Dr. Healy is legally required to rely on statistically significant studies which show a relative risk of at least 2.0, but the Court is also unpersuaded that Dr. Healy's heavy reliance on case reports is accepted methodology for determining the strength of the association.

Koch's postulates also ask whether the association is consistent with other research. Reference Manual at 162. Dr. Healy does not discuss other research. He only states that a connection between akathisia and SSRIs occurs more consistently than a connection between SSRIs and effective

treatment for depression. This appears to be a misapplication of Koch's postulates.

Koch's postulates provide that a scientist should rule out alternative explanations to avoid reaching an erroneous conclusions. See Reference Manual at 162. Dr. Healy omits this postulate from his application of Koch's postulates. The Court cannot determine whether the scientific community generally accepts this methodology. Further, while Dr. Healy opines that Matthew Miller would not have committed suicide but for Zoloft, his examination of Matthew Miller's medical history and psychological state appears cursory. Dr. Healy apparently relies most heavily on the notes taken by Matthew Miller's treating physician, even though his contact with Matthew Miller was not extensive. Dr. Healy also relies upon information from Matthew Miller's parents, to the exclusion of evidence from other sources which suggest the possibility of suicidal thoughts and behavior. The Court questions whether the reliance on medical notes, to

the apparent exclusion of other, more personal knowledge, is generally accepted methodology.

With Koch's postulates, Dr. Healy considers three factors – salience of the association, support by experiment, and support by experiment, and support by analogy. The Court is unsure whether such factors have been or currently are part of Koch's postulates. The postulates have changed over the years and certain factors, such as specificity of the association and existence of a dose-response relationship, are no longer very significant. See Reference Manual at 163-64.

On a global scale, Dr. Healy's application of Koch's postulates focuses on a connection between SSRIs and Akathisia. He rarely addresses a connection between SSRI and suicide or akathisia and suicide. Instead he uses Koch's postulates to find a casual association between SSRIs and Akathisia, then relies on the fact that it is :biologically plausible" that akathisia causes suicide. Dr. Healy apparently concludes that akathisia causes suicide because this association is plausible.

This conclusion can be tested, yet Dr. Healy cites no studies finding an association between akathisia and suicide. The Court questions whether proving a casual association in this manner is generally accepted bu the scientific community.

Also, the Court would find useful information concerning the proper balancing of Koch's postulates. It appears that each scientist must reach his or her own conclusion after applying the factors, but the Court wold like some information as to the reasonable scientific limits of this subjective judgment. In other words, does scientific community generally hold any beliefs about the level of proof that is required? Which factors are most important? What combinations of factors are generally sufficient to allow a finding of causation?

The Court has questions concerning Dr. Healy healthy volunteer study. Firs, the parties provide conflicting evidence regarding the need foe placebo control. Second, the parties provide conflicting evidence whether Dr. Healy's study is a sufficient basis for calculating any statistically significant

relative risk. An independent expert could provide information on both issues.

Having evaluated the record in regard to these issues, the Court might conclude that plaintiffs have failed to show that Dr. Healy's opinions are grounded in the methods and procedures of science, which are based on actual knowledge and not subjective to belief or unaccepted speculation, and sustain defendant's motion to exclude his testimony. To do so on this record, however, would effectively endorse Pfizer's scientific position - which in many respects appears to be extreme and incredible Pfizer's view of the applicable " science" is heavily slanted towards its self interest, and it appears to confuse the question whether Dr. Healy's testimony is admissible with the question whether Dr. Healy's testimony is sufficient to support a finding of liability. The Court suspects that the adversary process in this case has generated two versions of "science", neither of which accurately portrays the current knowledge and methodology in

the area in dispute. The Court believes that an independent expert will help the Court bridge the gap.

IT IS THEREFORE ORDERED that the parties show cause in writing, on or before September 1, 2000, whether the Court should employ an independent expert to assist the Court in addressing the issues raised by David Healy's testimony, and the questions regarding this testimony, the Court sees little alternative but to stay all proceedings in this action until the Court has resolved the difficult question whether Dr. Healy's opinion is admissible.

Dated this 18th day of August, 2000 at Kansas City, Kansas.

Kathryn H. Vratil
United States District Judge

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF KANSAS

MARK MILLER AND CHERYL MILLER INDIVIDUALLY AND MARK MILLER AS ADMINISTRATOR OF THE ESTATE OF MATTHEW MILLER, DECEASED	§	
Plaintiffs	§	NO. 99-2326 KHV
v.	§	
PFIZER, INC. (Roerig Division)	§	
Defendant	§	

ORDER APPOINTING INDEPENDENT EXPERTS

Pursuant to Rule 104 of the Federal Rules of Evidence and D.Kan.Rule 26.4, the Court appoints the following experts in this case:

John M. Davis, M.D.
Research Professor
Gillman Professor
University of Illinois at Chicago
Department of Psychiatry
UIC 912 South Wood Street
Chicago, IL 60612
Telephone (312) 996-7206
Email: webmaster@psych.uic.edu

John Concato, M.D., M.S., M.P.H.
Yale University School of Medicine
Robert Wood Johnson Clinical Scholars Program
333 Cedar Street; SHM IE-61
New Haven, CT 06510
Telephone (203) 737-1674
Fax (203) 785-3461
Email: john.concato@yale.edu

These experts ("the appointees") will serve as independent expert witnesses to advise the Court on scientific issues which pertain to the admissibility of the testimony by Dr. David Healy.[1]

Both parties have stipulated to the expert qualifications of the appointees. Both parties have had an opportunity to review the appointees' qualifications and to interview the appointees by telephone regarding their backgrounds, professional affiliations, prior professional involvement with the parties and the produce at issue, and any possible conflict of interest. Neither party objects to the appointment of either of the appointees.

Dr. David Healy is plaintiffs designated expert witness on the issue of medical causation. As described in the Court's order to show cause entered on August 18, 2000, Pfizer Inc. moved to exclude Dr. Healy's testimony on the grounds that (1) Dr. Healy's testimony will not assist the trier of fact because he is unable to show a statistically significant risk; (2) Dr. Healy improperly applied Koch's postulates; (3) Dr. Healy's testimony fails to satisfy the standards set out in *Daubert v. Merrell Dow*

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[1] A curriculum vitae for each of the experts is attached to this order.

Pharms. Inc., 509 U.S. 579 (1993); (4) Dr. Healy's opinions are not based on data reasonably relied upon in the fields of his testimony; and (5) Dr. Healy is unqualified to render opinions regarding warnings, regulatory matters, and suicidology. See Defendant's Pfizer Inc's Motion to Exclude the Testimony of David Healy (filed April 18, 2000). Plaintiffs opposed Pfizer's motion. See Plaintiffs' Brief in Support of Response to Pfizer Motion in Limine to Exclude Testimony of Dr. Healy (filed May 12, 2000). Pfizer filed its reply memorandum on May 26, 2000, completing the briefing of the subject motions. See Reply in Support of Defendant Pfizer Inc's Motion to Exclude the Testimony of David Healy (filed May 26, 2000).

On August 18, 2000, pursuant to D.Kan. Rule 26.4, this Court issued its order to show cause, stating that an independent expert witness would be helpful in determining whether Dr. Healy's methodology is proper under *Daubert*. In that order, the Court articulated specific scientific questions on which it believed advice from a court-appointed expert would be helpful. These questions were as follows:

1. Whether Dr. Healy's proffered methodology for determining medical causation can be and has been rested. (Order to Show Cause at 2).

2. Whether Dr. Healy's methodology or theory has been subject to peer review. (*Id.*)

3. The known or potential rate of error of Dr. Healy's methodology as he applied it. (*Id.*)

4. Whether Dr. Healy's methodology for determining medical causation has been generally accepted in the relevant scientific community. (*Id.*)

5. Whether Dr. Healy's heavy reliance on case reports is accepted methodology for determining the strength of the association that Dr. Healy opines exists between the use of Zoloft and suicide (*Id.* at 3.)

6. Whether, with respect to Dr. Healy's application of the Koch's postulates on consistency with other research, the circumstances that (i) Dr. Healy does not discuss other research, and (ii) Dr. Healy only states that a connection between akathisia and SSRIs occurs more consistently than a connection between SSRIs and effective treatment for depression, constitute a misapplication of the Koch's postulates. (*Id.*)

7. Whether the scientific community generally accepts Dr. Healy's methodology of omitting from his application of Koch's postulates the postulate that a scientist should rule out alternative explanations to avoid reaching an erroneous conclusion. (*Id.*)

8. Whether Dr. Healy's reliance on notes taken by Matthew Miller's treating physician and information from Matthew Miller's parents, to the exclusion of evidence from other sources which suggest the possibility of suicidal thoughts and behavior, is generally accepted methodology.

9. Whether three factors applied by Dr. Healy – salience of the association, support by experiment, and support by analogy – have been or currently are part of Koch's postulates. (*Id.*)

10. Whether Dr. Healy's manner of finding a causal association between use of SSRIs and akathisia, and akathisia and suicide, described in the first paragraph of page four of the Order to Show cause, is generally accepted by the scientific community. (*Id.*)

11. Whether scientific limits apply to subjective judgments derived from application of Koch's postulates, including whether the scientific community generally holds any beliefs about the level of proof that is required, which factors are most important, and what combinations of factors are generally sufficient to allow a finding of causation. (*Id.*)

12. Whether Dr. Healy's reliance on his healthy volunteer study is scientifically proper in the light of the absence of any placebo control. (*Id.*)

13. Whether Dr. Healy's health volunteer study is a sufficient basis for calculating any statistically significant relative risk. (*Id.*)

The Court requests that the appointees (1) analyze the materials which will be submitted to them (as described below) and (2) provide the court and parties, no later than **August 1, 2001**, a joint written report which expresses their scientific consensus, if they have one, and their individual, respective views in those instances in which they have no consensus, as to the answers to each of the questions presented in the Court's order to show cause and summarized above.

The fundamental question on which the Court seeks the appointees' advice is whether Dr. Healy's methodology, and his application of it in this case, constitute valid, scientifically reliable reasoning in support of his opinions that Zoloft cause suicide (general causation) and that Zoloft caused Matthew Miller's suicide (specific causation). To the extent that the appointees identify scientific issues, other than those referred to in the specific questions that the Court has posed above, that bear on the scientific reliability or unreliability of Dr. Healy's testimony, they are requested to address and express their opinions on those issues in their report, as well.

It is the Court's intention that the appointees provide the Court scientific advice pertaining to the scientific issues which have been raised in the parties' briefing and submissions on the admissibility of Dr. Healy's testimony. These issues, as described above, were fully briefed, and the parties were afforded full opportunity to adduce evidence in support of their respective positions, in April and May 2000. In addition, those materials were supplemented earlier this year by the filing of copies of a report submitted by Pfizer to the Irish Medicines Board in July 1999 and by that Board's letter to Pfizer regarding the report.

Regarding materials to be reviewed and analyzed by the appointees, the parties shall jointly provide each appointee:

(1) a copy of the parties' previously filed briefs pertaining to the motion to exclude Dr. Healy's testimony;

(2) a copy of all exhibits cited or referred to in those briefs, in the same form and sequence in which they were filed with the Court;[2]

(3) a copy of Pfizer's July 1999 report to the Irish Medicines Board; [3]

(4) the letter of January 2000 form the Irish Medicines Board to Pfizer regarding the report;[4] and

(5) Dr. Healy's Declaration of August, 2000, which addresses the concerns which the Court articulated in its order to show cause.

The transmittal letters which accompany these materials shall state only that the parties are jointly providing the materials pursuant to this order. All of the foregoing materials are to be provided to the appointees **no later than May 4, 2001**.

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[2] Specifically, these materials are to consist of (i) Defendant Pfizer Inc's Motion to Exclude the Testimony of David Healy (filed April 18, 2000) and the supporting legal memorandum; (ii) each exhibit cited in or submitted in support of that motion or memorandum; (iii) Plaintiff's Response to Pfizer Motion in Limine to Exclude Testimony of Dr. Healy (filed May 12, 2000) and their brief supporting the response; (iv) each exhibit cited in or submitted in support to that response and brief; (v) Pfizer's Reply in Support of Defendant Pfizer Inc's Motion to Exclude the Testimony of David Healy (filed May 26, 2000); and (vi) each exhibit cited in that reply memorandum.

[3] These materials shall be submitted in the form in which Pfizer provided them to the Irish Medicines Board.

[4] These materials shall be submitted in the form in which Pfizer received them from the Irish Medicines Board.

Unless ordered by this Court, no supplemental briefing, arguments, exhibits, evidence, or other written material shall be added to the submissions by either party. This facet of the Court's order is not intended, however, to preclude the appointees from considering relevant material which is not contained without the universe of the documents which the parties will submit.[5] In fact, the Court *encourages* and *expects* the appointees to examine whatever medical or scientific literature is necessary to render their professional opinions on the foregoing topics.[6] The appointees are authorized and encouraged to communicate with each other in any manner which is convenient for them.

If the appointees should conclude that it would be helpful to consult with one or more other medical or scientific personnel concerning this matter, they shall first notify the Court of the purpose of the desired consultation and identify the person or persons with whom they wish to consult, so that the presence or absence of any conflict pertaining to any such consultant can be assessed before the communication occurs. The Court considers it important that all bases for the opinions and advice ultimately expressed by the appointees be open and clear to the parties and the public, and that there be no communication with non-appointed persons that could lend even the appearance of any

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[5] For example, nothing in this order will prohibit the appointees from considering whether scientific opinion testimony must be based on a relative risk factor of 2.0 or greater or from reviewing peer reviewed scientific literature which has been published during the pendence of this action (including, without limitation, Donovan, et al., *"Deliberate Self-Harm and Antidepressant Drugs: Investigation,"* British J. Psych. 2000 Dec; 177 (6): 551-56, Table 3).

[6] To the extent practicable, the appointees' reports shall cite any publication and record evidence on which they rely to support particular statements or conclusions.

conflict of interest, improper influence or other impropriety to the work of the appointees.

During the pendency of this action, without leave of Court, the appointees shall not in any way or for any purpose contact, communicate with, or respond to any communication from any party or attorney, representative or expert witness for any party. If such a communication should be come necessary or desirable, the Court will supervise the communication, ensure the presence of all parties to the communication, and make appropriate provisions to transcribe or otherwise record any such communication.

If the appointees should have questions regarding any aspect of their work pursuant to this appointment, they are instructed to contact the Deputy Clerk Linda South at (913) 551-6550, and notify her of the nature of their inquiry. For routine or administrative matters which do not affect the substantive rights of any party, the Court will respond to the inquiry and notify the parties of any pertinent instructions or information provided to the experts. For the substantive inquiries, the Court will schedule a telephone conference or hearing to resolve the questions.

The appointees are requested to submit a joint written report to the Court **no later than August 1, 2001**. Triplicate originals of the report should be addressed to the Court and signed by both appointees. The appointees may organize and format their report in the manner they deem best suited for their task. **No lather than August 1, 2001**, the appointees shall also send one copy of their report by overnight delivery to each of the following lead attorneys for the parties.

Arnold Anderson Vickery, Esq.
Attorney for Plaintiffs
Vickery & Waldner, L.L.P.
2929 Allen Parkway, Suite 2410
Houston, Texas 77019
Telephone (713) 523-5939
Fax (713) 523-5939

Malcolm E. Wheeler, Esq.
Attorney for Pfizer Inc.
Wheeler Trigg & Kennedy, P.C.
1801 California Street, Suite 3600
Denver, Colorado 80202-2636
Telephone (303) 292-2525
Fax (303) 294-1879

The appointees are further directed to maintain in readily accessible files all documents, written materials, correspondence, notes, calculations, or other information which they receive, review or create in connection with their appointment. Those materials may be discoverable by the parties upon completion of the final report.

Pursuant to Rule 104 of the Federal Rules of Evidence, the Court will conduct a hearing on Pfizer's motion to exclude the testimony of Dr. Healy's testimony, including the appointees' evaluation of its scientific reliability, **at 1:30 p.m. on August 23, 2001.** The appointees are required to attend this hearing, to observe any testimony which Dr. Healy may present, and to testify regarding their independent evaluation of his methodology and reasoning in this action. Specific procedures to be followed in any such hearing may be announced by separate order. The Court hereby schedules a telephone conference of counsel for **August 3, 2001 at 9:30 a.m. Central**

Daylight Time. The purpose of that conference will be to discuss the procedures which will pertain to the hearing on August 27, as well and any discovery or other matters which will allow the parties to more fully prepare for that hearing.[7]

The appointees shall be compensated at the rate of $200.00 per hour for work in connection with this appointment, and shall be reimbursed for reasonable travel and administrative expenses. With their written report, they shall submit invoices for their fees and expenses. After the Court has discharged them from further duties, they shall submit final invoices for all additional fees and expenses. The Court will direct payment. Each party has agreed to, and shall bear half of the expenses of this procedure.

Dated this 24th day of April, 2001 at Kansas City, Kansas

Kathryn H. Vratil
United States District Judge

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[7] If the parties believe that they will wish to depose the appointees before the time of the scheduled hearing, they should jointly contact the appointees in the very near future to reserve available dates.

Supreme Court, U.S.
FILED
JUL 6 - 2004
OFFICE OF THE CLERK

No. 03-1505

IN THE

Supreme Court of the United States

MARK MILLER AND CHERYL MILLER, INDIVIDUALLY, AND MARK MILLER, AS ADMINISTRATOR OF THE ESTATE OF MATTHEW MILLER, DECEASED,

Petitioners,

v.

PFIZER INC (ROERIG DIVISION),

Respondent.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Tenth Circuit

RESPONDENT'S BRIEF IN OPPOSITION

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QUESTION PRESENTED

Whether this Court should review the court of appeals' decision affirming the entry of summary judgment against Petitioners when the district court (i) found the methodology used by Petitioners' causation expert unreliable and scientifically invalid; (ii) followed the recommendations of two court-appointed experts in doing so; (iii) found the opinions expressed by the expert to have been a "moving target" throughout the litigation, but nevertheless allowed him to revise his opinion numerous times and limited him only when he attempted to change his opinions yet again on the day of the *Daubert* hearing; (iv) granted summary judgment based on Petitioners' failure to adduce judicially cognizable evidence of medical causation; and (v) granted summary judgment on an alternative state-law ground independent of the failure to provide expert testimony on the medical-causation issue.

RULE 29.6 STATEMENT

Respondent Pfizer Inc ("Pfizer") is a publicly traded corporation. It has no parent corporation, and no publicly held company owns ten percent or more of its stock.

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IN THE

Supreme Court of the United States

No. 03-1505

MARK MILLER AND CHERYL MILLER, INDIVIDUALLY, AND MARK MILLER, AS ADMINISTRATOR OF THE ESTATE OF MATTHEW MILLER, DECEASED,

Petitioners,

v.

PFIZER INC (ROERIG DIVISION),

Respondent.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Tenth Circuit

RESPONDENT'S BRIEF IN OPPOSITION

Petitioners seek review of a narrowly fact-bound question: whether the district court abused its discretion when, against the background of the pretrial proceedings that had occurred, it enforced its own scheduling order and the requirements of Federal Rule of Civil Procedure 26(a)(2) to limit the evidence to be considered in ruling on the admissibility of a proffered expert's testimony under Federal Rules of Evidence 702 and 703. (*See* Pet. i, 13.) After carefully examining the proposed testimony of Petitioners' medical-causation expert as stated in multiple written submissions and in a two-day deposition, appointing two independent experts who then issued a de-

tailed written report finding the methodology used by Petitioners' expert unreliable and scientifically invalid, and conducting a two-day evidentiary hearing on the issue, the district court found the proposed testimony unreliable, scientifically invalid, and inadmissible. Because Petitioners had no other evidence of medical causation, the district court granted summary judgment for Pfizer.

On February 4, 2004, a unanimous panel of the United States Court of Appeals for the Tenth Circuit affirmed. Petitioners also seek review of the question whether the judgment should be reversed because of what they call a "pronouncement" by the United States Food and Drug Administration ("FDA") made on March 22, 2004 (*id.* at i), more than a month after the court of appeals' ruling, and "announcements" made by the FDA and the British Medicines Control Agency at various times more than a year after the district court's grant of summary judgment (*id.* at 1-3).

In short, Petitioners seek review of two narrowly fact-bound questions having no implications for the development of the law. In addition, there is no conflict in the lower courts on any legal issue presented by the facts of this case, and the rulings below are fully consistent with the applicable decisions of this Court.

STATEMENT OF THE CASE

Petitioners commenced this product liability action on July 27, 1999, alleging that Pfizer's prescription antidepressant Zoloft® had been sold without adequate warnings and had caused their clinically depressed son to commit suicide. On August 13, 1999, pursuant to Federal Rule of Civil Procedure 26(a)(2) and the district court's scheduling order, Petitioners disclosed that Dr. David Healy, a psychiatrist from rural North Wales in the United Kingdom, would be the expert witness whose testimony they would offer to show that Zoloft can cause suicide (general medical causation) and that it

did cause the suicide alleged in this case (specific medical causation).

Thereafter, as the district court later observed with judicial politesse, Dr. Healy's opinion on general medical causation "evolved throughout this litigation." *Miller v. Pfizer Inc*, 196 F. Supp. 2d 1062, 1066 n.10 (D. Kan. 2002). The evolution began with a supplemental report by Dr. Healy dated December 10, 1999, that, like his original report, provided no data analyses or calculations supporting his opinions. It continued with a letter report dated March 6, 2000, stating new purported bases for his opinions, again un-supported by data analyses or calculations. At his deposition on March 27 and 28, 2000, he again offered new relative-risk opinions, again unsupported by data analyses or calculations.

On April 18, 2000, within the time specified by the district court for the filing of dispositive motions, Pfizer moved, under Federal Rule of Evidence 702 and *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), to exclude Dr. Healy's medical-causation testimony. At the same time, Pfizer moved for summary judgment on the ground that, without Dr. Healy's testimony, Petitioners would have no evidence to prove general and specific medical causation. Petitioners then filed a declaration by Dr. Healy dated May 9, 2000, stating still more new purported bases for his opinions, but again unsupported by data analyses or calculations.

On August 18, 2000, the district court entered an order to show cause containing, *inter alia*, the following findings:

- "The first postulate [relied on by Dr. Healy] concerns the strength of the association between the exposure and effect. . . . [T]he court is . . . unpersuaded that Dr. Healy's heavy reliance on case reports is accepted methodology for determining the strength of the association." (Pet., Ex. 9 at 4.)

- "Koch's postulates also ask whether the association is consistent with other research. . . . Dr. Healy does not discuss other research. . . . This appears to be a misapplication of Koch's postulates." (*Id.* at 4-5.)
- "Koch's postulates provide that a scientist should rule out alternative explanations to avoid reaching an erroneous conclusion[]. . . . Dr. Healy omits this postulate from his application of Koch's postulates. . . . Further, while Dr. Healy opines that Matthew Miller would not have committed suicide but for Zoloft, his examination of Matthew Miller's medical history and psychological state appears cursory." (*Id.* at 5.)
- "This conclusion [of Dr. Healy's regarding a causal association between akathisia and suicide] can be tested, yet Dr. Healy cites no studies finding an association between akathisia and suicide." (*Id.* at 7.)

Despite these and other concerns expressed in the order regarding the unreliability and scientific invalidity of Dr. Healy's methodology, the district court, instead of granting Pfizer's *Daubert* motion, ordered the parties to "show cause in writing . . . whether the Court should employ an independent expert to assist the Court in addressing the issues raised by [that motion]." (*Id.* at 9.) In response to the order to show cause, Petitioners submitted not only a brief, but another declaration by Dr. Healy, dated August 31, 2000, purporting to address the methodological flaws and failure of proof that the district court had noted. Once again, however, Dr. Healy failed to provide data analyses or calculations.

The district court gave Petitioners another chance by appointing two independent experts—Dr. John Concato, a physician-epidemiologist from Yale Medical School, and Dr. John Davis, a neuropsychopharmacologist from the Univer-

sity of Illinois[1]—to help the court determine whether Dr. Healy's methodology was consistent with sound scientific principles. The independent experts were given Dr. Healy's deposition transcript, his reports, declarations, and exhibits, and the parties' briefing on the *Daubert* issue. *Miller v. Pfizer, Inc*, 356 F.3d 1326, 1329 (10th Cir. 2004). The district court also encouraged the independent experts to examine additional scientific and medical literature as they saw fit. *Id.*

The independent experts provided the court with their written report on September 5, 2001. It discredited Dr. Healy's methodology as unreliable and unscientific in multiple respects. *See id.* It found, for example, the following:

- His "methodology for determining medical causation has not been accepted in the relevant scientific community." *Miller v. Pfizer, Inc*, No. 99-CV-2326, 2001 WL 1793169, at *2 (D. Kan. Sept. 4, 2001).
- His "heavy reliance on case reports" was not accepted methodology for determining strength of a posited association between a drug and suicidality. "[L]ack of a comparison group would still make a series of case reports unsuitable for determining the quantitative strength of an association, regardless of other attributes." *Id.* at *2-3.
- His failure to discuss other research and demonstrate consistency with other research pertaining to his posited associations between Zoloft® and "akathisia" and between akathisia and suicide constituted misapplication of the scientific method. *Id.* at *6.

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[1] Petitioners recommended the appointment of Dr. Davis and agreed to the appointment of Dr. Concato.

- His failure to "rule out alternative explanations" for suicides temporally associated with therapy violated "a fundamental tenet of scientific reasoning." *Id.* at *4.

- His reliance on certain factual evidence and "exclusion of evidence from other sources which suggest the possibility of suicidal thoughts and behavior" that preceded and were independent of use of Zoloft® was "not generally accepted practice." *Id.* at *4-5.

- His "manner of finding a causal association between use of SSRIs and akathisia, and akathisia and suicide," was not "generally accepted by the scientific community." *Id.* at *6.

- "A threshold for level of proof [about causal relationships] is often established only after deliberation by selected members of the scientific field, as when scientific panels reach consensus. Regarding the question of SSRIs and suicide, such panels have not found the level of proof to be reached. Dr. Healy . . . holds a minority opinion in this matter. We acknowledge that a minority view (proposing causality) at one point in time may later become the majority view (that establishes causality), but that phenomenon has not, to date, occurred with regard to an association of sertraline and suicide." *Id.* at *7.

- "The data related to Dr. Healy's healthy volunteer study, as well as data from the so-called Hindmarch study, do not produce statistically significant results." *Id.* at *8.

- "[T]he available evidence does not show an increased rate of suicidal acts [or ideation] associated with SSRI agents. (The rate of suicide on SSRIs is actually decreased by approximately one-half)." *Id.* at *9.

- Dr. Healy's methods relied on unpublished data and "do not conform to generally accepted methodology" because "the numbers of patients in each group are not reported, and the statistical significance of the results . . . are not provided." *Id.* at *10.

- His "healthy volunteer study is not a sufficient basis for calculating any statistically significant relative risk, due to issues involving study design and sample size." *Id.* at *11.

- Regarding an article relied on by Dr. Healy: "As noted by the study authors, however, available data suggested that three possible confounding factors (age; antidepressant prescription switches; prior history of deliberate self-harm) contributed to an increased unadjusted relative risk [for SSRIs relative to other antidepressants]. . . . Thus, the study does not provide strong evidence for or against a possible sertraline-suicide association." *Id.* at *10.

- His "'lines of evidence' only partially satisfy Koch's postulates. . . . [and] 'confounding' has not been excluded. . . as an alternative explanation for an apparent sertraline-suicide relationship." *Id.* at *11.

Again, however, rather than granting Pfizer's *Daubert* motion at that point, the district court gave Petitioners yet another chance: it held a two-day evidentiary hearing on the motion on November 19-20, 2001. The court-appointed experts and Dr. Healy testified in response to questioning by each side's counsel, and the court-appointed experts even were permitted to engage in a dialogue with Dr. Healy to provide the court with additional information not elicited by counsel. When Petitioners and Dr. Healy attempted to introduce new relative-risk numbers purportedly based on new analyses and calculations derived from documents that Pfizer had produced to Petitioners nearly two years earlier, however,

Pfizer objected. The court sustained the objection, ruling that, under Federal Rule of Civil Procedure 26(a)(2), the time for disclosing opinions had long since passed, particularly because Dr. Healy sought to base his new opinions on information that had been produced to Petitioners before his deposition and before he had prepared and served his several supplemental written submissions. *Miller*, 356 F.3d at 1330.

After the hearing, consistent with the views of the independent experts, the district court concluded that Dr. Healy's methodology was unreliable and failed to reflect sound scientific principles. The court found that Dr. Healy had (a) misapplied or omitted six of the seven Koch's postulates (the scientific criteria comprising the methodology he claimed to have employed), (b) relied on scientifically flawed studies, (c) employed methodologies and espoused opinions not generally accepted in the relevant scientific community, and (d) simply ignored substantial evidence of alternative causes of the death in issue, including the decedent's depression and history of suicidal thoughts and expressions for many months before his treatment with Zoloft® commenced.

The district court noted that the flaws in Dr. Healy's methodology for finding general medical causation were "glaring, overwhelming and unexplained." *Miller*, 196 F. Supp. 2d at 1085. It also found that, on the subject of specific causation, Dr. Healy had given "scant attention to evidence of factors—other than Zoloft—which may have caused [decedent's] suicide. Dr. Healy's testimony on specific causation does not satisfy Rule 702 because it does not utilize sufficient facts and data and it is not the product of reliable principles and methods." *Id.* at 1087.

Because Dr. Healy's opinions were inadmissible, and because those opinions were Petitioners' only proffered evidence of medical causation, the district court granted summary judgment to Pfizer. The court also granted summary

judgment to Pfizer on the alternative ground that Petitioners could provide no facts to show that the decedent's treating physician would have changed his treatment of decedent had he received the different warnings that Petitioners advocated.

Petitioners appealed to the United States Court of Appeals for the Tenth Circuit, claiming that the district court had abused its discretion by limiting the information provided to the independent experts and by excluding Dr. Healy's testimony. *Miller*, 356 F.3d at 1331. Noting that "[t]he orderly conduct of litigation demands that expert opinions reach closure," *id.* at 1334, the court of appeals found no abuse of discretion. The court stated: "Far from improperly freezing Dr. Healy's opinions or holding him to his first Rule 26 statement, the district court allowed Dr. Healy to express revised opinions on numerous occasions. The district court exhibited patience and concern for fairness to both sides. It did not abuse its discretion." *Id.* at 1335. The court also concluded that the district court had "carefully and properly performed its gatekeeping function under *Daubert*." *Id.*

Because Petitioners had no admissible evidence of medical causation, the court of appeals held that the district court had properly granted summary judgment on that ground. The court of appeals did not rule on the district court's separate, additional basis for having granted summary judgment—namely, the absence of evidence that the allegedly inadequate warning was a proximate cause of the death in issue.

While the case was pending in the court of appeals, Petitioners filed two requests to take judicial notice of certain "facts" that they have argued in their Petition to this Court. The court of appeals denied those requests. *Id.* at 1336.

REASONS FOR DENYING THE PETITION

I. THE ISSUES PRESENTED IN THE PETITION ARE NOT OF A NATURE THAT WARRANTS DISCRETIONARY REVIEW BY THIS COURT.

The petition presents no issue that warrants review by this Court. Petitioners seek review essentially because they consider it unfair that the district court enforced its own scheduling order and Federal Rule of Civil Procedure 26(a)(2) and held Petitioners to their burden of proof under Federal Rule of Evidence 702 with respect to Dr. Healy's proposed testimony on the issue of medical causation. The petition cites no conflict among appellate court decisions, no controversial interpretation of this Court's jurisprudence, and no important issue of federal law. To the contrary, it complains of fairly commonplace *Daubert* and summary judgment rulings made unusual only by (i) the district court's patience in allowing Petitioners to make multiple supplemental submissions in an effort to provide at least minimal reliability and scientific validity to their expert's methodology, including submissions made up to two years after the expert's Rule 26(a)(2) report was due, and (ii) the district court's appointment of two independent experts to help evaluate the methodology used by Petitioners' expert.

The district court properly could have granted Pfizer's *Daubert* and summary judgment motions two years earlier, on August 18, 2000, when the court found that Petitioners had failed in several respects to show that Dr. Healy had followed the requirements of the methodology he had claimed to apply—namely, Koch's postulates—in formulating his opinions on the issue of medical causation. The district court again properly could have granted Pfizer's motions on September 5, 2001, when the court-appointed experts submitted their written report concluding that Dr. Healy's methodology was unreliable and unscientific in multiple respects. The district court's determination that it would not

allow Dr. Healy to change his opinions yet again and to ambush Pfizer's attorneys with new relative-risk numbers in support of his opinions on medical causation at the *Daubert* hearing in November 2001, more than two years after his Rule 26(a)(2) report was due, was nothing more than a straightforward—in fact, a long-delayed—enforcement of Rule 26(a)(2) and the court's own scheduling order. *See, e.g.*, Fed. R. Civ. P. 26(a)(2) advisory committee note ("[A] party will not ordinarily be permitted to use on direct examination any expert testimony not so disclosed.").

In sum, the petition does not ask this Court to review a rule of law. Instead, it asks this Court to reweigh the factual circumstances that the district court considered in deciding to enforce its own scheduling order and the timing requirements of Federal Rule of Civil Procedure 26(a)(2).

The petition also asks this Court to consider various "announcements" made by regulatory bodies more than a year after the district court had entered summary judgment and a "pronouncement" made by the FDA more than a month after the court of appeals had affirmed that judgment. Petitioners' contention apparently is that the "announcements" and "pronouncement" support Dr. Healy's proffered conclusions on the issue of medical causation.

That contention, however, rests on Petitioners' erroneous belief that the district court ruled Dr. Healy's testimony on medical causation inadmissible because his *conclusion* was incorrect. In fact, however, the court ruled his testimony inadmissible because his *methodology* was unreliable and unscientific. *See* 196 F. Supp. 2d at 1075-85. In any event, the "announcements" and "pronouncement" that Petitioners argue should be weighed in determining the reliability and scientific validity of Dr. Healy's opinions are evidence that did not even exist until long after the district court had entered its judgment. Accordingly, they cannot properly be considered as new evidence pertinent to the judgment. *See,*

e.g., Johnson v. Offshore Express, Inc., 845 F.2d 1347, 1358 (5th Cir. 1988) ("'Newly discovered evidence' under Rule 60(b)(2), however, must be evidence of facts existing at the time of the original trial." (internal citations omitted)); *Rivera v. M/T Fossarina*, 840 F.2d 152, 156 (1st Cir. 1988) ("evidence that came into existence after the court's judgment" was properly not considered in Rule 60(b) motion because it was not "newly discovered evidence" (internal citation and quotation marks omitted)); *Am. Motorists Ins. Co. v. Gen. Host Corp.*, 120 F.R.D. 129, 132 (D. Kan. 1988) (to be considered in Rule 59(e) motion, "the evidence must have existed at the time of trial, but not have been known to the movant").

Therefore, the petition should be denied because it does not present any issue that warrants this Court's attention.

II. REVIEW OF THE ISSUES PRESENTED IN THE PETITION COULD NOT CHANGE THE OUTCOME OF THIS CASE, BECAUSE THE DISTRICT COURT PROPERLY GRANTED SUMMARY JUDGMENT ON AN ADDITIONAL, ALTERNATIVE STATE-LAW GROUND.

This case also is not appropriate for review by this Court because review of the issues presented by the petition could not change the outcome of the case. Even if this Court were to grant the petition and resolve in Petitioners' favor the issues the petition raises, Petitioners still would be barred from proceeding in the district court because the district court granted summary judgment on an additional, alternative, independent ground not addressed by the petition.

To prove their case under applicable Kansas law, Petitioners had to establish that Zoloft® can cause suicide, that Zoloft® specifically caused Petitioners' decedent to commit suicide, and that the inadequate warnings were a cause in fact of the suicide. *See, e.g., Miller*, 196 F. Supp. 2d 1096, 1124

(D. Kan. 2002); *Wooderson v. Ortho Pharm. Corp.*, 681 P.2d 1038, 1045-49, 1057 (Kan. 1984). The district court properly ruled that Pfizer was entitled to summary judgment *both* because of Petitioners' failure of proof on the issue of medical causation *and* because Petitioners could not prove that the allegedly inadequate warnings were a cause in fact of the decedent's death. The latter, independent basis for the summary judgment entered below would be unaffected by any ruling on the issues presented by the petition.

Because Kansas law applies the "learned intermediary" doctrine, manufacturers of prescription drugs are only required to give warnings to medical providers, not directly to patients. *Wooderson*, 681 P.2d at 1052. Petitioners contended in the district court that inadequate Zoloft® warnings caused their decedent's death. Uncontroverted evidence showed, however, that even if the warnings accompanying the drug were inadequate, that inadequacy could not have been a cause in fact of the decedent's death. The physician who prescribed Zoloft® for the decedent provided uncontradicted testimony that he would have prescribed the medication and given the same instructions to Petitioners even if he had received the warning Petitioners claimed should have been given. That evidence broke the chain of causation and precluded any finding that the allegedly inadequate warning was a cause of the decedent's injury. *See, e.g., Eck v. Parke, Davis & Co.*, 256 F.3d 1013, 1018-19 (10th Cir. 2001); *Daniel v. Ben E. Keith Co.*, 97 F.3d 1329, 1332-33 (10th Cir. 1996). Accordingly, the district court granted summary judgment for Pfizer on this separate ground. *See Miller*, 196 F. Supp. 2d at 1126-30.

After affirming the district court's ruling with respect to the Healy testimony and the related grant of summary judgment, the Tenth Circuit did not reach the alternative summary judgment ruling based on the absence of proof of causation in fact. If this Court were to rule in favor of

Petitioners here, however, the Tenth Circuit would merely affirm the grant of summary judgment on the alternative basis. *See Ralston v. Smith & Nephew Richards, Inc.*, 275 F.3d 965, 977-78 (10th Cir. 2001); *Eck*, 256 F.3d at 1018-19; *Daniel*, 97 F.3d at 1332-33; *see also, e.g., Odom v. G.D. Searle & Co.*, 979 F.2d 1001, 1003-04 (4th Cir. 1992); *Willett v. Baxter Int'l, Inc.*, 929 F.2d 1094, 1098-99 (5th Cir. 1991).

Because another issue in this case would preclude Petitioners from going forward even if this Court were to rule in Petitioners' favor on the issues presented in the petition, there is no good reason for this Court to grant review.

III. THE DISTRICT COURT PROPERLY APPLIED THIS COURT'S PRECEDENTS AND FEDERAL RULE OF CIVIL PROCEDURE 26(a)(2).

In addition to presenting run-of-the-mill procedural and *Daubert* issues and ignoring the alternative basis for summary judgment, the petition fails to show any error by the district court or by the unanimous Tenth Circuit panel.

A. The District Court Did Not Abuse Its Discretion in Applying *Daubert* and Its Progeny.

The district court exhaustively reviewed Dr. Healy's various opinions, supporting documentation, and testimony. After that careful review, and with the benefit of testimony and a written report from two independent experts, the court ruled that Dr. Healy's methodology was unreliable and scientifically invalid. The court of appeals affirmed that ruling, and properly so.

This Court has made clear that "the trial judge must have considerable leeway in deciding in a particular case how to go about determining whether particular expert testimony is reliable." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999). Thus, reviewing courts must apply a deferential

abuse-of-discretion standard in reviewing a trial court's evidentiary decision. *See Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 143 (1997).

Here, the court of appeals held that the district court had not abused its discretion in applying *Daubert* principles. *See Miller*, 356 F.3d at 1335. Indeed, the court of appeals found that the district court had "carefully followed *Daubert* in determining whether Dr. Healy's opinions were founded on scientific principles," had done a "thorough" job, and had "properly performed its gatekeeping function." *Id.*

In the face of the district court's learned, detailed 32-page *Daubert* opinion and the court of appeals' approving review of that opinion, the best argument the petition can muster is that two other courts have allowed Dr. Healy to testify in other cases involving other drugs. (*See* Pet. 4, 6-7.) That argument fails both legally and factually.

Legally, even if the district court's ruling in this case were inconsistent with another district court's ruling in another case, the inconsistency would not signify any problem. It is well established that different courts may reasonably reach different results in evaluating the admissibility of expert testimony, and such differences do not reflect an abuse of discretion. *See, e.g., Hollander v. Sandoz Pharms. Corp.*, 289 F.3d 1193, 1206 (10th Cir.) ("*Daubert's* effort to safeguard the reliability of science in the courtroom may produce a counter-intuitive effect: different courts relying on . . . essentially the same science may reach different results."), *cert. denied*, 537 U.S. 1088 (2002).

Factually, the district court's decision here is not inconsistent with either of the two decisions cited by Petitioners in which Dr. Healy was allowed to testify. Neither in their petition nor in the courts below have Petitioners even attempted to show that the methodology used and conclusions reached by Dr. Healy in this case are the same as the

methodology used and the conclusions reached in those other cases. Nor could they have made such a showing. The two cases in which Dr. Healy was allowed to testify involved drugs other than Zoloft®, drugs with different chemical make-ups, different clinical trial results, different pharmacological properties, and different side-effect profiles.[2] It is well established that even slightly different chemical compounds can have different effects, and imputing the effects of one to another does not meet *Daubert's* reliability requirement. *See Hollander*, 289 F.3d at 1207. Moreover, by his own admission, Dr. Healy's opinions in this case differ significantly from those he gave in the other cases.

B. The District Court Did Not Abuse Its Discretion by Precluding Petitioners' Expert Witness from Springing New Purported Bases for His Medical-Causation Opinions on the Day of the *Daubert* Hearing and After Having Withheld Them from His Rule 26(a)(2) Report, from All of His Supplemental Submissions, and from His Deposition Testimony.

The district court recognized that Dr. Healy had made his opinions a "moving target throughout this litigation." Nevertheless, the court patiently allowed Dr. Healy to revise his opinions numerous times. The independent experts and the district court considered all of Dr. Healy's revisions up until the time of the *Daubert* hearing in November 2001. Only then did the district court draw the line and refuse to allow him to spring new opinions that he had withheld from his

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[2] One of the opinions cited by Petitioners is an unpublished opinion in *Cassidy v. Eli Lilly & Co.*, Civil Action No. 821 (W.D. Pa. May 30, 2002). The drug involved in that case was Prozac. The other opinion cited by Petitioners is in *Estates of Tobin by Tobin v. SmithKline Beecham Pharmaceuticals*, 164 F. Supp. 2d 1278 (D. Wyo. 2001). The drug in that case was Paxil.

Rule 26(a)(2) report, from all of his supplemental written submissions, and from his deposition testimony.

At the *Daubert* hearing and in a filing after the hearing, Petitioners attempted to introduce new calculations and graphs prepared by Dr. Healy. The new opinion evidence was based on evidence that Pfizer had produced to Petitioners nearly two years before the *Daubert* hearing. The district court found that "[a]ny calculations that . . . Dr. Healy wanted to make from this report could—and should—have been made *well before* this point in the litigation." *Miller*, 196 F. Supp. 2d at 1091 (emphasis in original). The court further noted that "Plaintiffs' counsel admitted that the graphs and calculations which he sought to introduce were not based on new scientific developments or new information from the experts." *Id.*

The district court properly recognized that the Federal Rules of Civil Procedure prohibit a party from making its expert's opinions a "moving target" that constantly evolves. The rules require that all bases for expert opinions be timely disclosed under Rule 26(a)(2) or they are inadmissible, absent substantial justification. *See* Fed. R. Civ. P. 26(a)(2) and advisory committee notes; Fed. R. Civ. P. 37(c)(1). The district court acted within its discretion in excluding Petitioners' untimely efforts to introduce new opinions by Dr. Healy proffered years *after* completion of the Rule 26(a)(2) disclosures, *after* Pfizer's *Daubert* motion and summary judgment motion had been fully briefed, and *after* the court-appointed experts had spent months evaluating the methodology and opinions in Dr. Healy's multiple written submissions and in his two-day deposition. *See, e.g., Miller*, 356 F.3d at 1334; *Jacobsen v. Deseret Book Co.*, 287 F.3d 936, 953-54 (10th Cir.), *cert. denied*, 537 U.S. 1066 (2002); *Lohnes v. Level 3 Communications, Inc.*, 272 F.3d 49, 59-61 (1st Cir. 2001) (affirming exclusion of untimely disclosed expert affidavit submitted in response to summary judgment motion and stating

that "expert disclosure requirements are not merely aspirational, and courts must deal decisively with a party's failure to adhere to them").

The district court's ruling also comports with this Court's recognition in *Daubert* that, while science can evolve over time, the law must make final determinations based on the evidence at a given point.

> It is true that open debate is an essential part of both legal and scientific analyses. Yet there are important differences between the quest for truth in the courtroom and the quest for truth in the laboratory. Scientific conclusions are subject to perpetual revision. *Law, on the other hand, must resolve disputes finally and quickly.* The scientific project is advanced by broad and wide-ranging consideration of a multitude of hypotheses, for those that are incorrect will eventually be shown to be so, and that in itself is an advance. Conjectures that are probably wrong are of little use, however, in the project of reaching a quick, final, and binding legal judgment—often of great consequence—about a particular set of events in the past. We recognize that, in practice, a gatekeeping role for the judge, no matter how flexible, inevitably on occasion will prevent the jury from learning of authentic insights and innovations. That, nevertheless, is the balance that is struck by Rules of Evidence *designed not for the exhaustive search for cosmic understanding but for the particularized resolution of legal disputes.*

Daubert, 509 U.S. at 596-97 (emphasis added). The need for finality in legal disputes involving "evolving" scientific research has been recognized by courts of appeals as well. *See, e.g., Allison v. McGhan Med. Corp.*, 184 F.3d 1300, 1322 (11th Cir. 1999); *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996) (noting that "the courtroom is not the place for scientific guesswork, even of the inspired sort"). Judge Posner's statement that "[l]aw lags science; it does not

lead it," *Rosen*, 78 F.3d at 319, succinctly summarizes the reality that Petitioners are unwilling to concede.[3]

The Federal Rules of Civil Procedure and the rulings of this Court make clear that the law must evaluate a scientific opinion at a fixed point in time and cannot allow that opinion to change constantly until final judgment has been entered. This is so because our system is designed to "reach[] a quick, final, and binding legal judgment—often of great consequence—about a particular set of events in the past." *Daubert*, 509 U.S. at 597. The district court carefully followed the Federal Rules of Civil Procedure and the dictates of this Court in fixing Petitioners' expert testimony at a point in time nearly two years after the date specified for expert disclosures. There was no abuse of discretion.

IV. THE FACTUAL ISSUES RAISED BY PETITIONERS PROVIDE NO BASIS FOR REVIEW.

Finally, Petitioners ask the Court to grant their petition because of purportedly "new" factual issues they seek to raise. As a general matter, factual issues rarely justify review by this Court. In this case, they most certainly do not.

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[3] Petitioners' selective quotation of Justice Breyer's remarks in the *Reference Manual on Scientific Evidence* (2d ed.), (*see* Pet. at 7-8), paints a misleading picture that is inconsistent with the principle of finality adopted by this Court in *Daubert*. Justice Breyer's views expressed in the introduction are consistent with the lower court rulings in this case. Justice Breyer wrote, "Our objective is to avoid legal decisions that reflect . . . so-called science. The law must seek decisions that fall within the boundaries of scientifically sound knowledge." *Reference Manual on Scientific Evidence* at 4 (2d ed. 2000). Furthermore, "[d]espite the difficulties, . . . there is an increasingly important need for law to reflect sound science." *Id.* at 5. An expert opinion that two eminent court-appointed experts found was not based on good science does not fall within the bounds of "scientifically sound knowledge" or "sound science."

Petitioners' theory seems to be that additional factual developments have occurred since the *Daubert* hearing that may change the district court's evaluation of Dr. Healy's opinions. Petitioners are wrong on both the law and the facts. Dr. Healy's opinions offered in the case were based on flawed methodology and junk science. That was the case in 2001, and it is still the case today. The methodology and junk science he in fact applied from 1999 to 2001 in this case have not subsequently changed, nor is it even possible for them to have done so, regardless of what may have happened in the world thereafter. He did what he did.

Furthermore, the alleged factual developments cited by Petitioners address only the issue of general medical causation. Dr. Healy's opinions regarding specific causation gave "scant attention to evidence of factors—other than Zoloft—which may have caused [decedent's] suicide. Dr. Healy's testimony on specific causation does not satisfy Rule 702 because it does not utilize sufficient facts and data and it is not the product of reliable principles and methods." *Miller*, 196 F. Supp. 2d at 1087. No announcement or pronouncement by the FDA or anyone else can change this.

Moreover, the recent FDA statements relied on by Petitioners do not, contrary to Petitioners' suggestion, establish general medical causation in this or any other case. The FDA's document attached as Exhibit 5 to Petitioner's Appendix states that "FDA has *not concluded that these drugs cause worsening depression or suicidality*, [but that] health care providers should be aware that worsening symptoms could be due to the underlying disease or *might* be a result of drug therapy." (Emphasis added.) Thus, the FDA has *not* concluded that general causation exists; rather, it has merely provided a precautionary measure that provides no support to Dr. Healy's conclusion, much less to his methodology. *See, e.g., Hollander*, 289 F.3d at 1215 (citing *Glastetter v. Novartis Pharms. Corp.*, 252 F.3d 986, 991 (8th Cir. 2001)).

As the Tenth Circuit noted in similar circumstances in *Hollander*, "differing standards militate against applying regulatory actions to the elements of tort law." 289 F.3d at 1215 (citing *Mitchell v. Gencorp Inc.*, 165 F.3d 778, 783 n.3 (10th Cir. 1999)). The fact that the government says that a drug *might* cause a certain reaction does not establish general causation for tort purposes.

Finally, as noted above, reversing the district court on the expert issue would not change the outcome of this case, since the very warnings alleged by Plaintiffs (and that Petitioners erroneously contend are involved in the Food and Drug Administration's recent pronouncements upon which Petitioners rely) were based on information well-known to the prescribing doctor in the case and would not have changed anything that the doctor did for the decedent or any of the warnings that he gave. Accordingly, the Court should deny the petition.[4]

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[4] Petitioners' suggestion that this case is appropriate for GVR misunderstands that doctrine. Typically, that procedure is employed when there has been some intervening Supreme Court precedent or legal development that justifies granting the petition, vacating the judgment, and remanding the case. *See Lawrence ex. rel. Lawrence v. Chater*, 516 U.S. 163, 165-66 (1996).

> Where intervening developments, or recent developments that [the Court has] reason to believe the court below did not fully consider, reveal a reasonable probability that the decision below rests upon a premise that the lower court would reject if given the opportunity for further consideration, and where it appears that such a redetermination may determine the ultimate outcome of the litigation, a GVR order is . . . potentially appropriate.

Id. at 167. Here, there is no reasonable probability that the district court would change its exhaustive analysis and decision based on the new "evidence," nor is there any chance that a changed decision on general medical causation would affect the district court's decision on specific causation or causation in fact. Thus, "the delay and further cost entailed in a remand are not justified by the potential benefits of further consideration by the lower court, [and] a GVR order is inappropriate." *Id.* at 168.

CONCLUSION

The petition for a writ of certiorari should be denied.

Respectfully submitted,

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